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(71) Applicant: **TAKEDA CHEMICAL INDUSTRIES,  
LTD.  
1-1, Doshomachi 4-chome  
Chuo-ku, Osaka 541 (JP)**

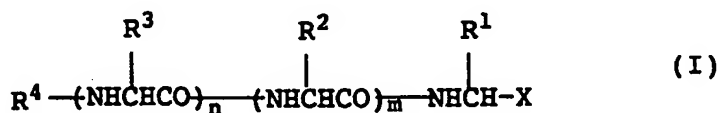
(72) Inventor: **Sohda, Takashi  
27-20, Higashikanmaki 2-chome  
Takatsuki, Osaka 569 (JP)  
Inventor: Fujisawa, Yukio  
1-31-104, Mikagenakamachi 4-chome  
Higashinada-ku, Kobe, Hyogo 658 (JP)**

Inventor: **Yasuma, Tsuneo  
20-5, Takada-cho  
Ibaraki, Osaka 567 (JP)  
Inventor: Mizoguchi, Junji  
18-D75-206, Tsukumodal 5-chome  
Suita, Osaka 565 (JP)  
Inventor: Kori, Masakuni  
20-4, Aoyama 5-chome,  
Shijimi-cho  
Miki, Hyogo 673-05 (JP)  
Inventor: Takizawa, Masayuki  
1-1-709, Shinoharaobanoyamacho 1-chome  
Nada-ku, Kobe, Hyogo 675 (JP)**

(74) Representative: **von Kreisler, Alek,  
Dipl.-Chem. et al  
Patentanwälte  
von Kreisler-Selting-Werner  
Bahnhofsvorplatz 1 (Delchmannhaus)  
D-50667 Köln (DE)**

(54) **Alcohol or aldehyde derivatives as cathepsin L inhibitor and bone resorption inhibitor.**

(57) The present invention provides a cathepsin L inhibitor containing a compound of the formula:



wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group which may be substituted; R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom or a hydrocarbon residue which may be substituted; R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group which may be substituted; X is formula: -CHO or -CH<sub>2</sub>OB (wherein B is a hydrogen atom or a protecting group of hydroxyl group); m and n independently are an integer of 0 or 1; provided that R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl, or a carbamoyl or thiocarbamoyl group which may be substituted when R<sup>1</sup> is an unsubstituted lower alkyl, arylalkyl on methylthioethyl group, R<sup>2</sup> and R<sup>3</sup> independently are a lower alkyl or arylalkyl, X is -CHO, m is 1 and n is 0 or 1, or a salt thereof.

Compound (I) is useful as a prophylactic/therapeutic agent for osteoporosis.

**EP 0 611 756 A2**

Field of the Invention

The present invention relates to a cathepsin L inhibitor and bone resorption inhibitor containing an alcohol or aldehyde derivative, or salt thereof as an active ingredient.

Background of the Invention

Osteoporosis is a pathologic state or disease involving some symptom or risk due to quantitative bone reduction exceeding a certain degree. Major symptoms are spinal kyphosis, fractures of dorsolumbar bones, vertebral centra, femoral necks, lower end of radius, ribs, upper end of humerus, and others. In normal bone tissue, bone destruction occurs constantly, but there is good balance between bone formation and resorption; osteoblasts and osteoclasts play key roles in bone formation and bone resorption, respectively. Upon deterioration of this balance, bone resorption surpasses bone formation, resulting in quantitative bone reduction. Drugs suppressing bone resorption are therefore expected to serve well in preventing and treating osteoporosis. Traditionally, bone resorption-suppressing agents such as estrogens and calcitonin have been used to treat osteoporosis. However, these therapeutic agents fail to achieve satisfactory effect in some cases, due to subject limitations or uncertain efficacy. There is therefore need of a new prophylactic/therapeutic method for accentuated bone resorption.

It has recently been shown that cathepsin L, a protease secreted by osteoclasts in the process of bone resorption, is integrally involved in the decomposition of collagen, a bone supporting protein. Presumably therefore, bone collagen decomposition due to bone resorption can be prevented by inhibiting cathepsin L activity, a means useful in the prevention and treatment of osteoporosis. Epoxysuccinic acid derivatives, such as those disclosed in Japanese Patent Unexamined Publication Nos. 304074/1990, 304075/1990 and 304085/1990 are known to exhibit cathepsin L inhibitory action.

Traditionally, leupeptin and antipain have been known to inhibit protease activity, and various compounds have been synthesized as aldehyde derivatives from amino acids. For example, acetyl-Leu-Leu-tryptophanal, acetyl-Leu-Leu-phenylalaninal etc. are disclosed as chymotrypsin inhibitors in Biochemical and Biophysical Research Communications, Vol. 49, p. 343 (1972). Peptide-derived phenylalaninal and tryptophanal derivatives are disclosed as chymotrypsin inhibitors and myodystrophy remedies in PCT Int. Appl. WO 8400365. Also, PCT Int. Appl. WO 9214696 and PCT Int. Appl. WO 9204045 disclose the anti-HIV activity of peptide-derived phenylalaninal derivatives and the CCK (cholecystokinin) antagonist activity of N-acyltryptophanal, respectively. EP-A2-0 504 938 discloses a use for prophylaxis or treatment of bone disease of peptidic aldehyde derivatives based on their hypocalcemic effect.

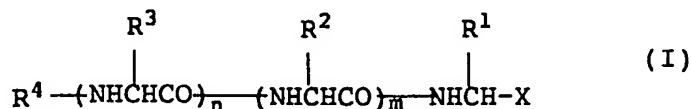
However, the above epoxysuccinic acid derivatives inhibit not only cathepsin L but also other proteases, as disclosed in the above patent publications, thus lacking practical applicability to prophylactic/therapeutic drugs for osteoporosis. And the cathepsin L inhibitory activity are not disclosed in the above documents of the peptide derivatives.

Summary of the Invention

The present inventors sought to develop a more commonly applicable drug showing selective inhibition of cathepsin L and direct action on the bone to suppress bone resorption, and found that an alcohol and aldehyde derivative represented by the following general formula (I) shows potent cathepsin L inhibition and direct action on the bone to excellently suppress bone resorption. The inventors made further investigations based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

(1) a cathepsin L inhibitor containing a compound of the formula:



wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group which may be substituted; R<sup>2</sup> and R<sup>3</sup>, independently are a hydrogen atom or a hydrocarbon residue which may be substituted; R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group which may be substituted; X is formula: -CHO or -CH<sub>2</sub>OB (wherein B is a hydrogen atom or a protecting group of

hydroxyl group); m and n independently are an integer of 0 or 1; provided that R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl or a carbamoyl or thiocarbamoyl group which may be substituted when R<sup>1</sup> is an unsubstituted lower alkyl, arylalkyl or methylthiomethyl group, R<sup>2</sup> and R<sup>3</sup> independently are a lower alkyl or arylalkyl group, X is -CHO, m is 1 and n is 0 or 1, or a salt thereof,

(2) A bone resorption inhibitor containing the compound of the formula (I) or a salt thereof,

(3) A compound of the formula (I) or a salt thereof,

(4) The compound of (3) wherein R<sup>1</sup> is an indolyl-lower alkyl,

(5) The compound of (3) wherein R<sup>1</sup> is a naphthyl-lower alkyl,

(6) The compound of (3) wherein R<sup>1</sup> is a phenyl-lower alkyl,

(7) The compound of (3) wherein R<sup>1</sup> is a hydrogen or lower alkyl,

(8) The compound of (3) wherein R<sup>2</sup> is a branched lower alkyl,

(9) The compound of (3) wherein R<sup>2</sup> is a phenyl-lower alkyl,

(10) The compound of (3) wherein R<sup>3</sup> is a branched lower alkyl,

(11) The compound of (3) wherein R<sup>3</sup> is hydrogen,

(12) The compound of (3) wherein R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group substituted by an alkyl, aryl, arylalkyl or alicyclic hydrocarbon group,

(13) The compound of (12) wherein R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl or a carbamoyl or thiocarbamoyl group which may be substituted,

(14) The compound wherein X is -CHO or -CH<sub>2</sub>OH,

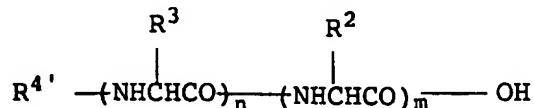
(15) The compound of (3) wherein m is 1 and n is 1,

(16) The compound of (3) wherein m is 1 and n is O,

(17) The compound of (3) wherein m is O and n is O,

(18) The compound of (3) wherein R<sup>1</sup> is a lower alkyl which may be substituted by indolyl; R<sup>2</sup> is a lower alkyl; R<sup>4</sup> is a naphthylsulfonyl or dibenzylacetyl; X is -CHO or -CH<sub>2</sub>OH; m is O or 1 and n is O,

(19) A method of producing the compound as defined in (3) which comprises reacting a compound of the formula:

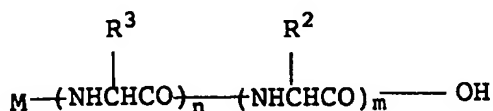


wherein R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom a hydrocarbon residue which may be substituted; R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy group which may be substituted, or its reactive derivative with a compound of the formula:



wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group which may be substituted, and if desired, subjecting to an oxidation reaction or a reaction of protecting a hydroxyl group, and

(20) A method of producing the compound as defined in (3) which comprises reacting a compound of the formula:



wherein R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom or a hydrocarbon residue which may be

substituted, M is a protecting group of amino group; m and n independently are an integer of 0 or 1, or its reactive derivative with a compound of the formula:



wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group, subjecting to deprotecting reaction, to acylation, sulfonylation, oxycarbonylation, carbamoylation or thiocarbamoylation reaction in this order, and if desired, subjecting to an oxidation reaction or a reaction of protecting a hydroxyl group.

#### Brief Description of the Drawing

Figure 1 is a construction scheme for the plasmids obtained in Experimental Examples 4 and 5.

#### Description of the Preferred Embodiments

In the present specification, the constituent amino acids are of the L-configuration, unless otherwise stated. When shown by abbreviations, their notation is in accordance with the IUPAC (International Union of Pure and Applied Chemistry)-IUB (International Union of Biochemistry) Biochemical Nomenclature, e.g., Gly for glycine, Leu for leucine and Ile for isoleucine. Amino-protecting groups known to those skilled in the art are used. Preferable amino-protecting groups include acetyl, benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, t-butoxycarbonyl, phthalyl and formyl, with preference given to benzyloxycarbonyl or t-butoxycarbonyl.

With respect to formula (I) above, the arylalkyl group for R<sup>1</sup>, which may be substituted for, is exemplified by phenyl, naphthyl, anthryl, phenanthryl and acenaphthylene, and monocyclic or condensed polycyclic aromatic hydrocarbon groups resulting from binding of an aromatic hydrocarbon ring residue having 6 to 14 carbon atoms and a lower alkylene having 1 to 4 carbon atoms, such as benzyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl,  $\alpha$ -naphthylmethyl,  $\alpha$ -naphthylethyl,  $\beta$ -naphthylmethyl and  $\beta$ -naphthylethyl etc.

The heterocyclic alkyl group for R<sup>1</sup>, which may be substituted for, is exemplified by those resulting from binding of an aromatic heterocyclic ring residue as exemplified below and a lower alkyl having 1 to 4 carbon atoms. The aromatic heterocyclic ring residue is exemplified by 5- to 7-membered heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, 5- to 6-membered heterocyclic groups containing 2 to 4 atoms of nitrogen and 5- or 6-membered aromatic heterocyclic groups containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxygen. These aromatic heterocyclic groups may have condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-membered ring containing 1 atom of sulfur. Aromatic heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazolyl, benz[b]furanyl, isobenzofuranyl, benz[b]thienyl, 1H-pyrrolo[2,3-b]pyridin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyrazin-2-yl etc.

The lower alkyl group for R<sup>1</sup>, which may be substituted for, is exemplified linear or branched C<sub>1-6</sub> alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, 4-methylpentyl, 1, 1-dimethylbutyl, 2, 2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl etc.

The aryl group or aromatic heterocyclic ring residue in the arylalkyl group or aromatic heterocyclic alkyl group and lower alkyl group for R<sup>1</sup>, which may be substituted for, may have 1 to 3 substituents at any positions thereon. These substituents are exemplified by aliphatic chain hydrocarbon groups, alicyclic hydrocarbon groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen atoms, nitro groups, amino groups which may be substituted for, acyl groups which may be substituted for, hydroxyl groups which may be substituted for, thiol groups which may be substituted for and carboxyl groups which may be esterified.

Such aliphatic chain hydrocarbon groups include linear or branched aliphatic hydrocarbon groups such as alkyl groups, preferably those having 1 to 10 carbon atoms, alkenyl groups, preferably those having 2 to 10 carbon atoms, and alkynyl groups. Preferable alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl. Preferable alkenyl groups include vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl. Preferable alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne and 5-hexyne etc.

Such alicyclic hydrocarbon groups include saturated or unsaturated alicyclic hydrocarbons such as cycloalkyl groups, cycloalkenyl groups and cycloalkadienyl groups. Preferable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl. Preferable cycloalkenyl groups include 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl. Preferable cycloalkadienyl groups include 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl etc.

Such aryl groups are monocyclic or condensed polycyclic aromatic hydrocarbon groups, preferably phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl and others, with preference given to phenyl, 1-naphthyl, 2-naphthyl and others.

Preferable aromatic heterocyclic groups include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolyl, quinazolyl, quinoxalyl, phthalazinyl, naphthyliziny, purinyl, pteridinyl, carbazolyl,  $\alpha$ -carbolinyl,  $\beta$ -carbolinyl,  $\gamma$ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxthynyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indoliziny, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl etc.

Such halogens include fluorine, chlorine, bromine and iodine, with preference given to fluorine and chlorine.

Such hydroxyl groups include the hydroxyl group and hydroxyl groups having an appropriate substituent, particularly a substituent for use as a hydroxyl-protecting group, such as alkoxy, alkenyloxy, aralkyloxy and acyloxy, as well as aryloxy. Said alkoxy is preferably an alkoxy having 1 to 10 carbon atoms (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy). Said alkenyloxy is exemplified by those having 1 to 10 carbon atoms such as allyloxy, crotyloxy, 2-pentenyl, 3-hexenyl, 2-cyclopentenylmethoxy and 2-cyclohexenylmethoxy. Said aralkyloxy is exemplified by phenyl-C<sub>1-4</sub> alkyloxy (e.g., benzyloxy, phenethyloxy). Said acyloxy is preferably an alkanoyloxy having 2 to 4 carbon atoms (e.g., acetyloxy, propionyloxy, n-butyryloxy, isobutyryloxy). Said aryloxy is exemplified by phenoxy and 4-chlorophenoxy.

Such thiol groups include the thiol group and thiol groups having an appropriate substituent, particularly a substituent for use as a thiol-protecting group, such as alkylthio, aralkylthio and acylthio. Said alkylthio is preferably an alkylthio having 1 to 10 carbon atoms (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio). Said aralkylthio is exemplified by phenyl-C<sub>1-4</sub> alkylthios (e.g., benzylthio, phenethylthio). Said acylthio is preferably an alkanoylthio having 2 to 4 carbon atoms (e.g., acetylthio, propionylthio, n-butyrylthio, isobutyrylthio etc.).

Such amino groups include amino groups (-NH<sub>2</sub> groups) substituted for by 1 or 2 of alkyl groups having 1 to 10 carbon atoms, alkenyl groups having 1 to 10 carbon atoms, aromatic groups and acyl groups (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino, benzoylamino etc.).

Such acyl groups include formyl and groups resulting from binding of an alkyl having 1 to 10 carbon atoms, alkenyl having 1 to 10 carbon atoms or aromatic group and a carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanoyl, cyclopentanoyl, cyclohexanoyl, cycloheptanoyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl etc.).

Such esterified carboxyl groups (carbonyloxy groups) include those resulting from binding of a carboxyl group and an alkyl group having 1 to 6 carbon atoms, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl and hexyloxycarbonyl, those resulting from binding of a carboxyl group and an alkenyl group having 3 to 6 carbon atoms, such as allyloxycarbonyl, crotyloxycarbonyl, 2-pentenylloxycarbonyl and 3-hexenylloxycarbonyl, and those resulting from binding of a carbonyl group and an aralkyl group such as benzyloxycarbonyl and phenetyloxycarbonyl.

With respect to formula (I) above, the hydrocarbon residue for  $R^2$  or  $R^3$ , which may be substituted for, is exemplified by arylalkyl groups which may be substituted for and aliphatic hydrocarbon groups which may be substituted for. Such arylalkyl groups which may be substituted for include the same arylalkyl groups, which may be substituted for, as specified for  $R^1$  above. Such aliphatic hydrocarbon groups which may be substituted for include linear or branched saturated aliphatic hydrocarbon residues having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl and octyl, unsaturated aliphatic hydrocarbon residues having 2 to 8 carbon atoms, such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl, saturated alicyclic hydrocarbon residues having 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, unsaturated alicyclic hydrocarbon residues having 5 to 7 carbon atoms, such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl, and groups which result from binding of one of the above-mentioned alicyclic hydrocarbon residues and a saturated aliphatic hydrocarbon residue and which have 4 to 9 carbon atoms, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aliphatic hydrocarbon group for  $R^2$  or  $R^3$ , which may be substituted for, may have 1 to 3 substituents at any positions thereon. These substituents are exemplified by the same halogen atoms, nitro groups, amino groups which may be substituted for, acyl groups which may be substituted for, hydroxyl groups which may be substituted for, thiol groups which may be substituted for and carboxyl groups which may be esterified, as specified as substituents on the aryl or aromatic heterocyclic residue ring in the arylalkyl group or aromatic heterocyclic alkyl group for  $R^1$ , which may be substituted for.

The alkanoyl group, carbonyloxy group and sulfonyl group for  $R^4$  and  $R^4$  are represented by  $-\text{COR}^5$ ,  $-\text{COOR}^6$  and  $-\text{SO}_2\text{R}^7$ , respectively. The carbamoyl and thiocarbamoyl group for  $R^4$  are represented by  $\text{CONHR}^8$  and  $-\text{CSNHR}^9$ , respectively. ( $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$ , whether identical or not, independently represent a hydrocarbon residue which may be substituted for).

The hydrocarbon residue for  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  or  $R^9$ , which may be substituted for, is exemplified by aliphatic hydrocarbon groups, aromatic hydrocarbon groups and heterocyclic groups. Such aliphatic hydrocarbon groups are exemplified by the same examples as those given above for the aliphatic hydrocarbon group for  $R^2$  or  $R^3$ , which may be substituted for. Such aromatic hydrocarbon groups are exemplified by the same examples as those given above for the aryl group in the arylalkyl group for  $R^1$ .  $R^2$  or  $R^3$ , which may be substituted for. Such heterocyclic groups are exemplified by non-aromatic heterocyclic groups such as oxylanyl, azetidiny, oxetanyl, thietanyl, pyrrolidiny, tetrahydrofuryl, thiolanyl, piperiziny, tetrahydropyrany, morpholiny, thiomorpholiny, piperaziny, homopiperiziny, pyrroliny and imidazoliziny, as well as by the same examples as those given above for the aromatic heterocyclic residues on the aromatic heterocyclic alkyl group for  $R^1$ , which may be substituted for. These non-aromatic heterocyclic groups may be condensed with a benzene ring, a 6-membered ring containing 2 or less atoms of nitrogen or a 5-membered ring containing 1 atom of sulfur. Specifically, such condensed non-aromatic heterocyclic groups include chromanyl, isochromanyl, thiochromanyl and isothiochromanyl. The aliphatic hydrocarbon groups, aromatic hydrocarbon groups and heterocyclic groups mentioned above to exemplify the hydrocarbon residue for  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  or  $R^9$ , which may be substituted for, may have 1 to 3 substituents at any positions thereon. Such substituents are exemplified by the same examples as those given above for the substituent on the aryl group in the arylalkyl group for  $R^1$ , which may be substituted for.

With respect to X above, B for a protecting group of by hydroxyl group in formula :  $-\text{CHO}$  or  $-\text{CH}_2\text{OB}$  is exemplified those protecting groups of hydroxyl group in the hydroxyl group as a substituent of lower alkyl group of  $R^1$  mentioned above, preferably alkanoyl group of 2 to 10 carbon atoms.

Regarding the protecting group of amino group represented by M, mention is made those of amino-protecting groups disclosed herein before.

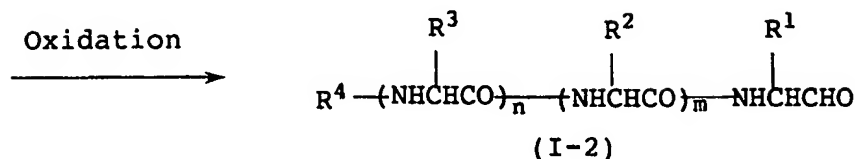
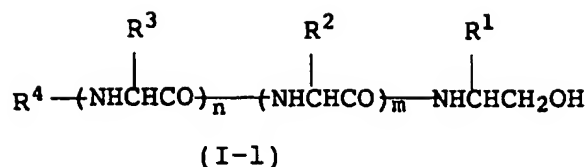
In the present invention, the salt of the compound of general formula (I) is preferably a physiologically acceptable salt, exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids. Preferable salts with inorganic bases include alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as calcium salt and magnesium salt, aluminum salt and ammonium salt. Preferable salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine etc. Preferable salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Preferable salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid etc. Preferable salts with basic amino acids include salts with arginine, lysine and ornithine. Preferable salts with acidic amino acids include salts with aspartic acid and glutamic acid.

With respect to compound (I), R<sup>1</sup> is preferably C<sub>1-6</sub> alkyl which may be substituted by indolyl or aryl, especially indol-3-ylmethyl, benzylmethyl, methyl, isopropyl, 1-naphthyl or the like, R<sup>2</sup> is preferably branched C<sub>3-6</sub> alkyl, phenyl-C<sub>1-6</sub> alkyl or hydrogen atom, especially sec-butyl, benzyl, hydrogen atom or the like, R<sup>3</sup> is preferably branched C<sub>3-6</sub> alkyl, especially sec-butyl, hydrogen atom, R<sup>4</sup> is preferably those being lower (C<sub>1-6</sub>) alkyl which may be substituted by aryl or alicyclic hydrocarbon-alkyl or aryl which may be substituted as respective R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup>, and is more preferably a C<sub>2-6</sub> alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group which is substituted by C<sub>1-6</sub> alkyl, aryl, arylalkyl or cycloalkyl, especially an alkanoyl group substituted by C<sub>3-12</sub> aryl or a sulfonyl, carbamoyl or thiocarbamoyl group substituted by aryl of more than 9 carbon atoms or C<sub>1-6</sub> alkyl. R<sup>4'</sup> is preferably those being lower (C<sub>1-6</sub>) alkyl which may be substituted by aryl or alicyclic hydrocarbon-alkyl or aryl which may be substituted as respective R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>, and is more preferably a C<sub>2-6</sub> alkanoyl, sulfonyl or carbonyloxy group which is substituted by C<sub>1-6</sub> alkyl, aryl, arylalkyl or cycloalkyl, especially an alkanoyl group substituted by C<sub>3-12</sub> aryl or a sulfonyl group substituted by aryl of more than 9 carbon atoms or C<sub>1-6</sub> alkyl. X is preferably -CHO or -CH<sub>2</sub>OH, m is preferably 0 or 1 and n is preferably 0.

Particularly preferable compounds of general formula (I) include N-(4-toluenesulfonyl)-(L)-isoleucyl-(L)-tryptophanal, N-(t-butoxycarbonyl)-(L)-isoleucyl-(L)-tryptophanal, N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanal, N-benzyloxycarbonyl-(L)-isoleucyl-(L)-isoleucyl-(L)-tryptophanal, N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-isoleucyl-(L)-tryptophanal, N-benzylcarbamoyl-(L)-isoleucyl-(L)-tryptophanal, N-[(2-cyclohexylethyl)carbamoyl]-(L)-isoleucyl-(L)-tryptophanal, N-(3-trifluoromethylphenylcarbamoyl)-(L)-isoleucyl-(L)-tryptophanal, N-(2-propylpentanoyl)-(L)-tryptophanal, N-dibenzylacetyl-(L)-tryptophanal, N-dibenzylacetyl-(L)-phenylalanyl, N-benzyloxycarbonyl-(L)-isoleucyl-(L)-phenylalanyl, N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-phenylalanyl, N-(1-naphthylsulfonyl)-(L)-isoleucylalanyl, N-benzyloxycarbonyl-(L)-leucyl-(L)-leucylglycinal, N-(2-propylpentanoyl)-(L)-alanyl-(L)-tryptophanal, N-(2-propylpentanoyl)-(L)-valyl-(L)-tryptophanal, N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanol, N-dibenzylacetyl-(L)-tryptophanol and N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-alaninol.

Production methods for compound (I) are hereinafter described in detail.

## Method A



In the above formulas, the symbols have the same definitions as those shown above.

This oxidation is carried out by a known oxidizing reaction. Such reactions include chromic acid oxidations such as Jones' oxidation, using chromium oxide-sulfuric acid-pyridine, Collins oxidation, using chromium-pyridine complex, oxidation with pyridinium chlorochromate (PCC) and oxidation with pyridinium dichromate (PDC), oxidation with activated DMSO and oxidation with oxoammonium salt.

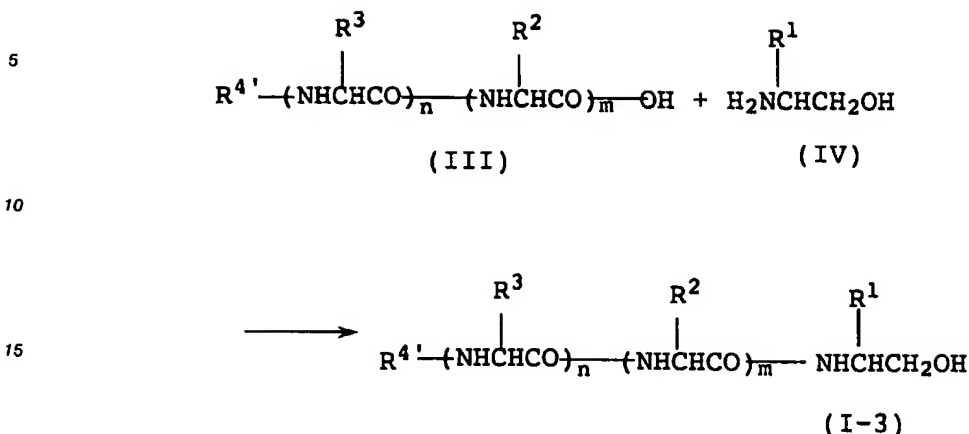
In the case of an optically active configuration, this oxidation is advantageously carried out by activated dimethyl sulfoxide (DMSO) oxidation. Activated DMSO oxidation is carried out in a solvent in the presence of both DMSO and an electrophilic reagent. This solvent is exemplified by ethers such as ethyl ether, isopropyl ether, tetrahydrofuran and dioxane, aromatic hydrocarbons such as benzene, toluene and xylene, N,N-dimethylformamide (DMF), halogenated hydrocarbons such as chloroform and dichloromethane, pyridine and dimethyl sulfoxide, chosen as appropriate according to the kind of electrophilic reagent. Methods of activated DMSO oxidation include the dicyclohexylcarbodiimide (DCC) method, the acetic anhydride method, the phosphorus pentoxide method, the chlorine method, the sulfur trioxide-pyridine method, the keteneimineenamine method and the mercury (II) acetate method, named according to the electrophilic reagent used. This oxidation is advantageously carried out by the sulfur trioxide-pyridine method, in which oxidation is achieved using a sulfur trioxide-pyridine complex as a DMSO activator reagent in the presence of triethylamine. This reaction can also be carried out with dimethyl sulfoxide as a solvent. The amount of triethylamine and sulfur trioxide-pyridine complex used is 1 to 10 mol, preferably 2 to 5 mol per mol of compound (I-1). Reaction temperature is -70 to 80 °C, preferably -20 to 40 °C, reaction time being 0.5 to 10 hours.

Aldehyde derivative (I-2) thus obtained may be isolated and purified by known means of separation and purification such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, redissolution and chromatography.

Starting material compound of the Method A can, for example, be produced as follows:



## Method B



In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (III) or its reactive derivative (or salt thereof) is reacted with compound (IV) or its derivative reactive at the amino group thereof (or salt thereof) to yield compound (I-3). Preferable derivatives of compound (IV) reactive at the amino group thereof include Schiff's base type imino or enamine form tautomeric isomers resulting from reaction of compound (IV) and a carbonyl compound such as aldehyde or ketone, silyl derivatives resulting from reaction of compound (IV) and a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide or bis(trimethylsilyl)urea, and derivatives resulting from reaction of compound (IV) and phosphorus trichloride or phosgene. Preferable salts of compound (IV) and its reactive derivatives are exemplified by the same acid adduct salts as specified for compound (I) above.

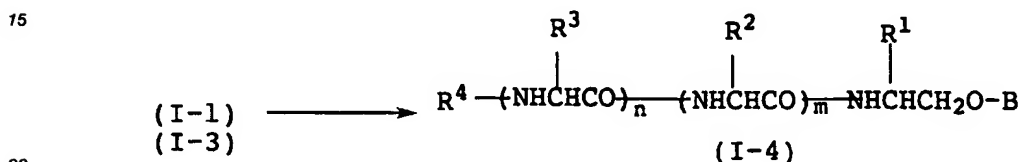
Preferable derivatives of compound (III) reactive at the carboxyl group thereof include acid halides, acid anhydrides, activated amides and activated esters. Other preferable reactive derivatives include acid chlorides, acid azides, mixed acid anhydrides such as those with a substituted phosphoric acid such as dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid or halogenated phosphoric acid, or with dialkylphosphorous acid, sulfurous acid, thiosulfuric acid or sulfuric acid, or with a sulfonic acid such as methanesulfonic acid, or with an aliphatic carboxylic acid, such as acetic acid, propionic acid, butyric acid, isobutyropivalic acid, pentanoic acid, isopentanoic acid or trichloroacetic acid, or with an aromatic carboxylic acid such as benzoic acid, symmetric acid anhydrides, activated amides with imidazole, 4-substitutional imidazole, dimethylpyrazole, triazole or tetrazole, activated esters such as cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl ester, vinyl ester, propargyl ester, p-nitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl ester, p-cresylthio ester, carboxymethylthio ester, pyranil ester, pyridyl ester, piperidyl ester and 8-quinolylthio ester, and esters with N-hydroxy compounds such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide and 1-hydroxy-1H-benzotriazole. These reactive derivatives can be optionally chosen according to kind of compound (III) used. Preferable salts of reactive derivatives of compound (III) include salts with bases, exemplified by alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as calcium salt and magnesium salt, ammonium salt, and organic base salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt and N,N-dibenzylethylenediamine salt. This reaction is normally carried out in an ordinary solvent such as water, an alcohol such as methanol or ethanol, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide or pyridine, but can be carried out in any other organic solvent, as long as it does not interfere with the reaction. These ordinary solvents may be used in mixture with water.

When compound (III) is used in the form of free acid or salt thereof, this reaction is preferably carried out in the presence of an ordinary condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, N,N'-carbonylbis-(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, ethox-

yacetylene, 1-alkoxy-1-chloroethylene, trialkyl phosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus oxychloride, diphenylphosphorylazide, thionyl chloride, oxalyl chloride, a lower alkyl haloformate such as ethyl chloroformate or isopropyl chloroformate, triphenylphosphine, 2-ethyl-7-hydroxybenzoxazolium salt, 2-ethyl-5-(m-sulphophenyl)isoxazolium hydroxide intramolecular salt, N-hydroxybenzotriazole, 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, or what is called Wilsmeier's reagent as prepared by reaction of N,N-dimethylformamide and thionyl chloride, phosgene, trichloromethyl chloroformate or phosphorus oxychloride. This reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal hydrogen carbonate tri(lower)alkylamine, pyridine, N-(lower)-alkylmorpholine or N,N-di(lower)alkylbenzylamine. Although reaction temperature is not subject to limitation, this reaction is normally carried out under cooling to heating conditions.

Compounds (I-1) and (I-3) are converted to compound (I-4).

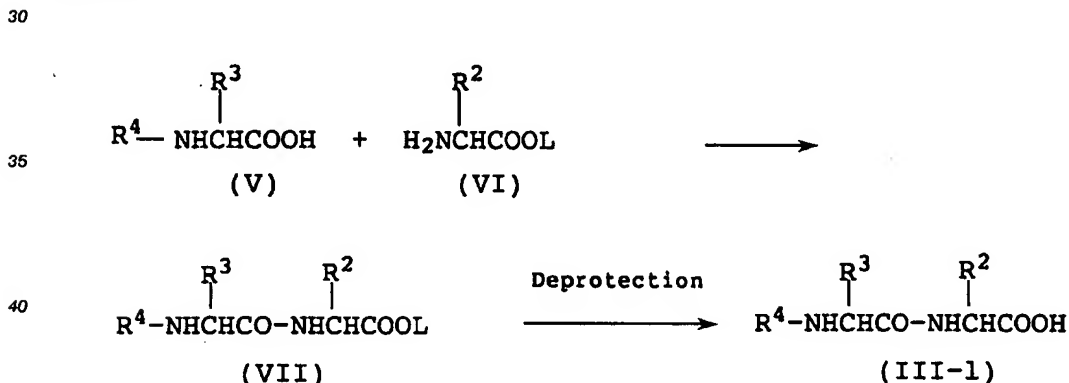
#### Method C



In the above formula, B is a protective group for hydroxyl group and the other symbols have the same definition as those shown above.

The reaction is conducted by reacting B-OH or its reactive derivative or its salt with compound (I-1) or its salt. This reaction is conducted as the same manner as the reaction of compound (III) or its reactive derivative of carboxyl group with compound (IV).

#### Method D



In the above formulas, L represents a carboxy-protecting group; the other symbols have the same definitions as above.

The carboxy-protecting group for L is exemplified by protecting groups in common use in the field of peptide synthesis, such as ester derivatives.

In this method, compound (V) or its derivative reactive at the carboxyl group thereof (or salt thereof) is reacted with compound (VI) or its derivative reactive at the amino group thereof (or salt thereof) to yield compound (VII), which is then subjected to a deprotecting reaction to remove the carboxy-protecting group to yield compound (III-1). The reaction of compound (V) or its derivative reactive at the carboxyl group thereof (or salt thereof) and compound (VI) or its derivative reactive at the amino group thereof (or salt thereof) is carried out in the same manner as method B.

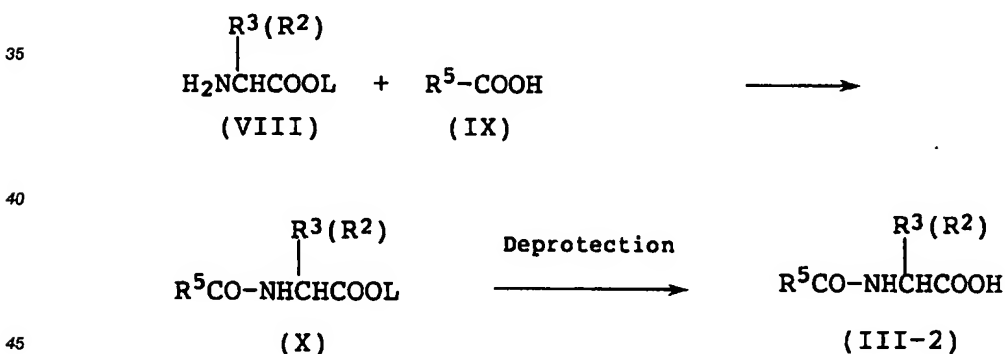
The deprotecting reaction of compound (VII) to remove its carboxy-protecting group can be achieved by any common method of carboxy protective group-removing reaction, such as deprotection by hydrolysis, reduction or Lewis acid. When the carboxy-protecting group is an ester, it can be removed by hydrolysis or

deprotection using Lewis acid, preferably hydrolysis in the presence of a base or acid. Preferable bases include inorganic bases such as alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxides (e.g., magnesium hydroxide, calcium hydroxide), alkali metal carbonates (e.g., sodium carbonate, potassium carbonate), alkaline earth metal carbonates (e.g., magnesium carbonate, calcium carbonate), alkali metal bicarbonates (e.g., sodium bicarbonate, potassium bicarbonate), alkali metal acetates (e.g., sodium acetate, potassium acetate), alkaline earth metal phosphates (e.g., magnesium phosphate, calcium phosphate), alkali metal hydrogen phosphates (e.g., disodium hydrogen phosphate, dipotassium hydrogen phosphate), and organic bases such as trialkylamines (e.g., trimethylamine, triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]non-5-ene and 1,8-diazabicyclo[5,4,0]-7-undecene. Hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or mixture thereof. Preferable acids include organic acids (e.g., formic acid, hydrobromic acid, sulfuric acid).

This hydrolysis is normally carried out in an organic solvent, water or a mixture thereof. Reaction temperature, not subject to limitation, is chosen as appropriate according to kind of carboxy-protecting group and method of deprotection. Deprotection using a Lewis acid is achieved by reacting compound (VII) (or salt thereof) with a Lewis acid such as a boron trihalide (e.g., boron trichloride, boron trifluoride), a titanium tetrahalide (e.g., titanium tetrachloride, titanium tetrabromide), an aluminum trihalide (e.g., aluminum chloride, aluminum bromide) or a trihaloacetic acid (e.g., trichloroacetic acid, trifluoroacetic acid). This deprotecting reaction is preferably carried out in the presence of a cation capturing agent (e.g., anisole, phenol) and normally carried out in a solvent which does not interfere with the reaction, such as a nitroalkane (e.g., nitromethane, nitroethane), an alkylene halide (e.g., methylene chloride, ethylene chloride), diethyl ether or carbon disulfide. These solvents may be used in mixture.

Deprotection by reduction is preferably applied to removing the protecting groups such as esters of haloalkyls (e.g., 2-iodoethyl, 2,2,2-trichloroethyl) and esters of aralkyls (e.g., benzyl). Methods of reduction for this deprotecting reaction include reduction with a combination of a metal (e.g., zinc, zinc amalgam) or a chromium compound salt (e.g., chromium (II) chloride, chromium (II) acetate) and an organic or inorganic acid (e.g., acetic acid, propionic acid, hydrochloric acid), and ordinary catalytic reduction in the presence of an ordinary metal catalyst (e.g., palladium-carbon, Raney nickel). Although reaction temperature is not subject to limitation, this reaction is normally carried out under cooling, room temperature or heating conditions.

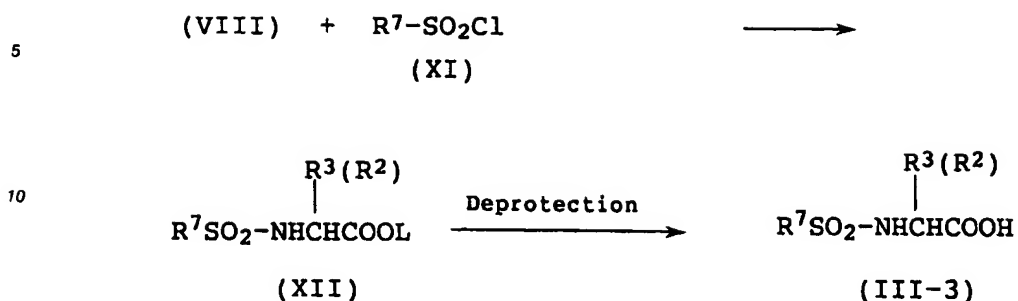
#### Method E



In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (IX) or its activated derivative at the carboxyl group thereof (or salt thereof) is reacted with compound (VIII) or its activated derivative at the amino group thereof (or salt thereof) to yield compound (X), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-2). This method is carried out in the same manner as method D.

## Method F

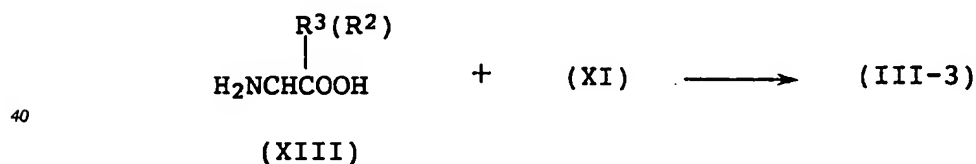


In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (XI) (or salt thereof) is reacted with compound (VIII) (or salt thereof) to yield compound (XII), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-3). The reaction of compounds (VIII) with (XI) is carried out in an appropriate solvent. This solvent is exemplified by aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as dioxane, tetrahydrofuran and dimethoxyethane, alcohols such as methanol, ethanol and propanol, ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanone and mixtures thereof.

The reaction of compounds (VIII) with (XI) is carried out in the presence of an appropriate base exemplified by alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogen carbonate, amines such as pyridine, triethylamine and N,N-dimethylaniline, sodium hydride and potassium hydride. The amount of these bases used is preferably about 1 to 5 mol per mol of compound (VIII). The reaction is carried out at temperatures of normally from -20 to 150°C, preferably from about -10 to 100°C. Compound (XII) thus obtained is subjected to a deprotecting reaction to yield compound (III-3). This deprotection is carried out in the same manner as the deprotecting reaction in method D.

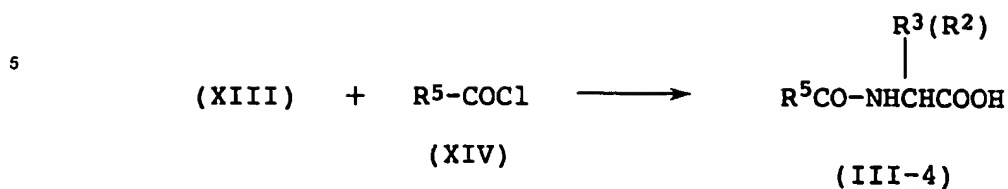
## Method G



In the above formulas, the symbols have the same definitions as those shown above.

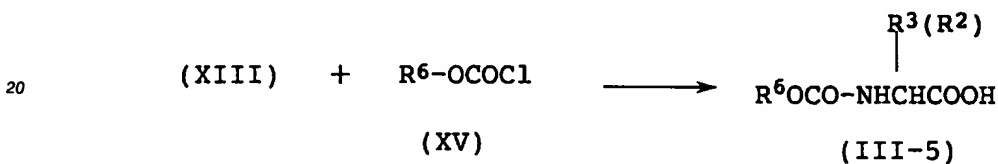
In this method, compound (XIII) (or salt thereof) is reacted with compound (XI) (or salt thereof) to yield compound (III-2). This sulfonylation is normally carried out under what is called Schotten Baumann's conditions, in which amino acid derivative (XIII), prepared as a sodium salt in an aqueous solution, is reacted with compound (XI) and then acidified.

### Method H



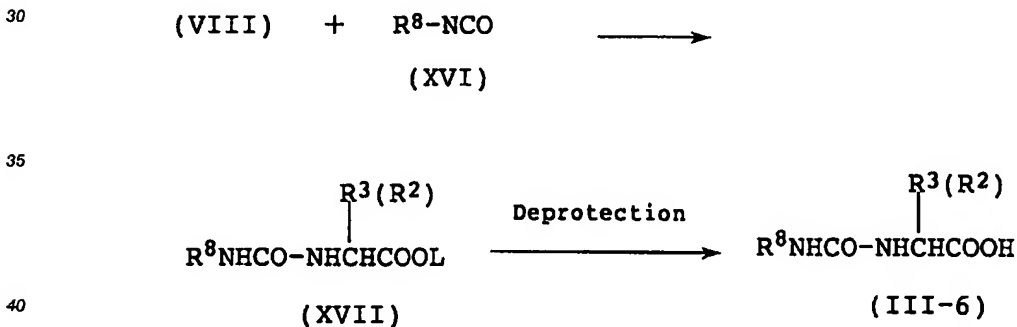
In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (XIII) (or salt thereof) is reacted with compound (XIV) (or salt thereof) to yield  
15 compound (III-4). This acylation is carried out in the same manner as method G. Method I



25 In the above formulas, the symbols have the same definitions as those shown above.

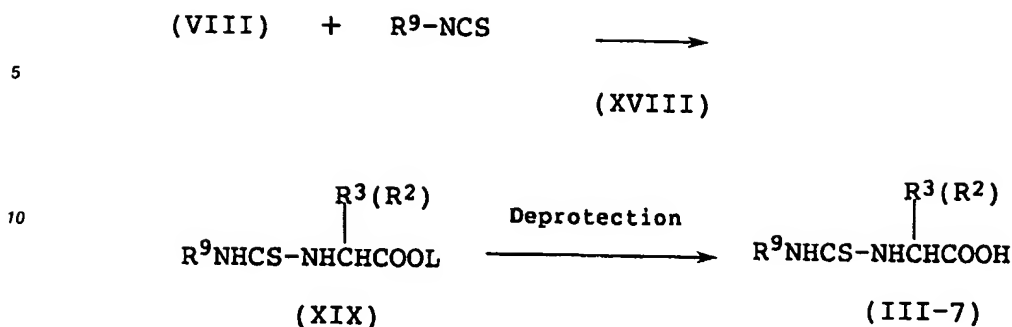
In this method, compound (XIII) (or salt thereof) is reacted with compound (XV) (or salt thereof) to yield compound (III-5). This method is carried out in the same manner as method H. Method J



In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (VIII) (or salt thereof) is reacted with compound (XVI) to yield compound (XVII), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-5). The reaction of compound (VIII) (or salt thereof) and compound (XVI) is carried out in an appropriate solvent. This solvent is exemplified by aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as dioxane, tetrahydrofuran and dimethoxyethane, ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanone and mixtures thereof. The amount of compound (XVI) used is preferably about 1 to 5 mol per mol of compound (VIII). The reaction is normally carried out at temperatures of -20 to 150°C, preferably about -10 to 100°C. Compound (XVII) thus obtained is subjected to a deprotecting reaction to yield compound (III-6). This deprotection is carried out in the same manner as the deprotection in method D.

## Method K

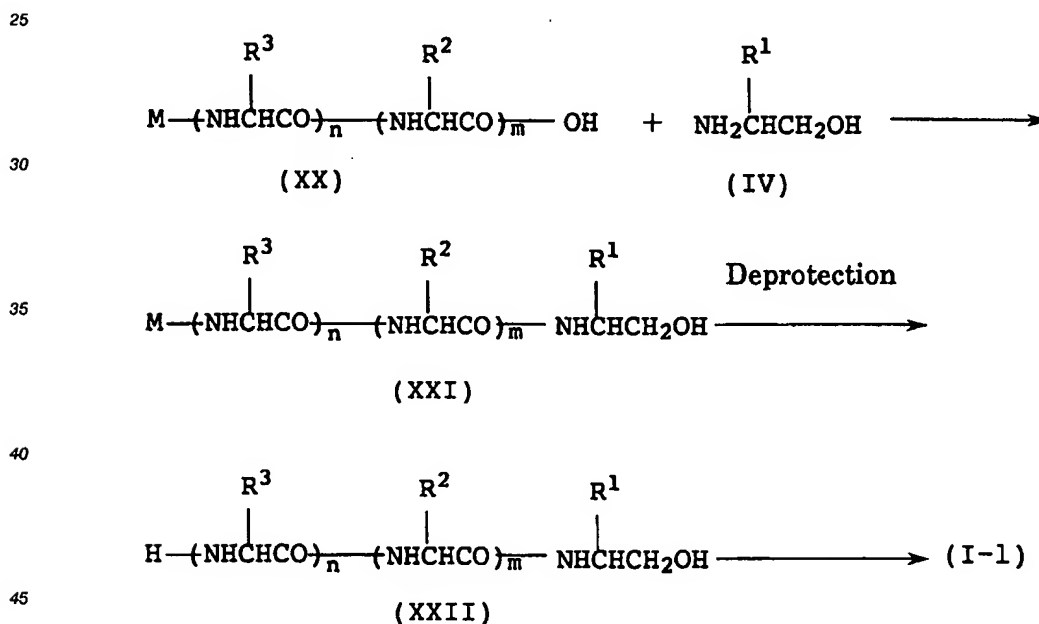


In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (VIII) (or salt thereof) is reacted with compound (XVIII) to yield compound (XIX), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-7). This reaction is carried out in the same manner as method J.

Starting material compound (I-1) for methods A and C can also be produced as follows:

## Method L



In the above formulas, M represents an amino-protecting group; the other symbols have the same definitions as those shown above.

The amino-protecting group for M is exemplified by protecting groups in common use in the field of peptide synthesis, such as oxycarbonyl derivatives, with preference given to benzyloxycarbonyl.

In this method, compound (XX) or its derivative reactive at the carboxyl group thereof (or salt thereof) is reacted with compound (IV) or its derivative reactive at the amino group thereof (or salt thereof) to yield compound (XXI), which is then subjected to a deprotecting reaction to remove its amino-protecting group to yield compound (XXII). The reaction of compound (XX) or its derivative reactive at the carboxyl group thereof (or salt thereof) with compound (IV) or its derivative reactive at the amino group thereof (or salt thereof) is carried out in the same manner as method B. In the amino-protecting group removing reaction of

compound (XXI), the amino-protecting group can be removed by any commonly used method of reaction to remove the amino-protecting group. For example, the benzyloxycarbonyl group is removed by catalytic reduction in the presence of a commonly used metal catalyst (e.g., palladium-carbon, Raney nickel). Reaction temperature is not subject to limitation; the reaction is normally carried out under cooling, room temperature or heating conditions. Then, compound (XXII) is acylated in the same manner as the reaction of compounds (VIII) and (IX) in method E or the reaction of compounds (XIII) and (XIV) in method H, sulfonated in the same manner as the reaction of compounds (VIII) and (XI) in method F, then oxycarbonylated in the same manner as the reaction of compounds (XIII) and (XV) in method I, carbamoylated in the same manner as the reaction of compounds (VIII) and (XVI) in method J, and then thiocarbamoylated in the same manner as the reaction of compounds (VIII) and (XVIII) in method K, to yield compound (I-1).

In the present invention, the compound of formula (I) can be administered orally or parenterally, as formulated by admixing an effective dose with a physiologically acceptable carrier, excipient or diluent in the form of solid preparations such as tablets, capsules, granules and powders, or liquid preparations such as syrups and injectable preparations.

Pharmaceutically acceptable carriers are various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders and disintegrating agents for solid preparations, and solvents, dissolution aids, suspending agents, isotonicizing agents, buffers and soothing agents for liquid preparations. Other pharmaceutical additives such as preservatives, antioxidants, coloring agents and sweetening agents may be used as necessary. Preferable excipients include lactose, sucrose, D-mannitol, starch, crystalline cellulose and light silicic anhydride. Preferable lubricants include magnesium stearate, calcium stearate, talc and colloidal silica. Preferable binders include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyvinylpyrrolidone. Preferable disintegrating agents include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, crosscarmellose sodium and carboxymethyl starch sodium. Preferable solvents include water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil. Preferable dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate. Preferable suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol, and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Preferable isotonicizing agents include sodium chloride, glycerol and D-mannitol. Preferable buffers include buffer solutions of phosphates, acetates, carbonates and citrates. Preferable soothing agents include benzyl alcohol. Preferable preservatives include p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid. Preferable antioxidants include sulfites and ascorbic acid.

The compound of formula (I) potently inhibits cathepsin L, excellently suppresses bone resorption and is of low toxicity. The compound of general formula (I) can therefore be used to prevent or treat osteoporosis in mammals (e.g., mice, rats, rabbits, dogs, cats, bovines, swines, humans).

When using as a prophylactic/therapeutic agent, compound (I) (or salt thereof) is administered at 1 to 500 mg, preferably 10 to 200 mg daily for each adult in the case of oral administration.

The action of compound (I) is hereinafter described by means of the following experimental examples.

#### Experimental Example 1: Cloning of cathepsin L cDNA of human renal origin

To amplify human cathepsin L cDNA by the PCR method, four primers were synthesized in accordance with a reported base sequence of cathepsin L of human renal origin [S. Gal and M.M. Gottesman, *Biochem. J.*, 253, 303 (1988)] as follows:

Sense primer No. 1:

5'-TTTTCAGGGGCGAGTAAGAT-3'  
(Sequence ID No. 1)

Sense primer No. 2:

5'-pCCGGATCCGGCTTTTATAGGATTGGTCTA-3'  
(Sequence ID No. 2)

Antisense primer No. 3:

5'-GGGGGCTGGTAGACTGAAGA-3'

(Sequence ID No. 3)

Antisense primer No. 4:

5'-pCCGGATCCATTCTCCCATGCATGCGCC-3'

(Sequence ID No. 4)

3 µl of a solution of the human renal cDNA library λ gt11 (CLONTECH Laboratories, Inc.) and 50 µl of distilled water were mixed. After incubation at 95 °C for 5 minutes, the mixture was immediately cooled in ice. Two primers (Nos. 1 and 3 above, 50 pmol of each) were added, and PCR was carried out as directed in the instruction manual for the kit supplied from Cetus/Perkin-Elmer, in which a series of reactions at 94 °C for 1 minute, 55 °C for 2 minutes and 72 °C for 3 minutes was repeated in 50 cycles. To the reaction mixture were added two other primers (Nos. 2 and 4 above, 50 pmol of each), and PCR was carried out in the same manner as above. The PCR product was separated by electrophoresis on 1.2% agarose gel; an amplified DNA fragment was seen at a position corresponding to the size (1132 bp) expected from the base sequence of cathepsin L of human renal origin. This DNA fragment was recovered from the gel and subcloned to the plasmid vector pBluescript<sup>®</sup> II SK + (produced by STRATAGENE). The base sequence of the cDNA portion, determined by the dideoxynucleotide synthetic chain termination method [J. Messing et al., *Nucleic Acids Res.*, 9, 309 (1981)], proved identical with the reported sequence. The plasmid containing this cDNA fragment was named pHCL-5.

#### Experimental Example 2: Expression of human cathepsin L in *Escherichia coli* MM294(DE3)

The cDNA of Experimental Example 1 was cleaved with restriction enzyme EcoRI and a 798 bp fragment (which encodes a part of the human cathepsin L precursor and the whole matured human cathepsin L) was recovered. To both ends of this fragment was ligated a BamHI linker (5'-pCCCGGATCCGGG-3'; sequence ID No. 5); the ligation product was inserted to the plasmid vector pET-3c for expression in *Escherichia coli* [Methods in Enzymology, ed. D.V. Goeddel, 185, 68, Academic Press (1990)]. The thus-constructed plasmid was designated pET-HCLα. *Escherichia coli* MM294(DE3) was transformed with pET-HCLα to express human cathepsin L in the presence of the T7 promoter [Methods in Enzymology, 185, 60(1990)]. The thus-obtained *Escherichia coli* transformant [*Escherichia coli* JM109/pTBN-HCLneo, harboring the plasmid pTBN-HCLneo, has been deposited under accession number IFO 15341 at the Institute for Fermentation, Osaka, since June 12, 1992, and under accession number FERM BP 3897 at the Fermentation Research Institute, Agency of Industrial Science and Technology since June 22, 1992.] was cultured; cells were disrupted by sonication and subjected to SDS-PAGE; a unique band appeared near 30 kDa, corresponding to human cathepsin L. Since the expressed product formed an inclusion body, human cathepsin L was partially purified from the precipitated fraction of the ultrasonically disrupted transformant.

#### Experimental Example 3: Preparation of antiserum to recombinant human cathepsin L

The partially purified recombinant human cathepsin L described in Reference Example 2 was mixed with an equal volume of Freund's complete adjuvant and about 1 ml was inoculated to a rabbit. Later, a mixture of a partially purified human cathepsin L and an equal volume of Freund's incomplete adjuvant was injected thrice at 10-day intervals, and blood was collected seven days after final injection. The obtained blood was kept standing at 37 °C for 30 minutes and then at 4 °C overnight, after which it was centrifuged to yield a human cathepsin L antiserum.

#### Experimental Example 4: Preparation of recombinant DNA for expression of human cathepsin L gene in animal cells

After the plasmid pHCL-5 (described in Experimental Example 1) was digested with restriction enzyme BamHI, a fragment of human cathepsin L cDNA was recovered by agarose gel electrophoresis. Next, this cDNA fragment was inserted to the restriction enzyme BglII site of the vector pTB551 for transient expression in animal cells [prepared by converting the EcoRI site to BglII site in the plasmid pTB389 described by Ono et al. in *Science*, 236, 1116(1989)] by the action of T4 DNA ligase and ATP, to yield the



expression plasmid pTB-HCL. MuLV-LTR was inserted between the restriction enzyme HindIII and ClaI sites of pTB-HCL to yield the expression plasmid pTBN-HCL (Figure 1).

Experimental Example 5: Preparation of recombinant DNA for expression of human cathepsin L gene in animal cells

To obtain an animal cell line that stably expresses human cathepsin L, the drug resistance marker neo gene was inserted to the vector pTBN-HCL described in Experimental Example 4 as follows: Namely, a fragment comprising the SV40 early promoter and the neo gene was inserted between the restriction enzyme ClaI and Sall sites of the plasmid pTBN-HCL to yield the plasmid pTBN-HCLneo (Figure 1).

Experimental Example 6: Expression of human cathepsin L gene in animal cells

Using the plasmid described in Experimental Example 5 (pTBN-HCLneo), mouse myeloma Sp2/0 cells were transformed as follows: Sp2/0 cells, cultivated in an ASF104 medium supplemented with 5% FCS (5% FCS/ASF medium), were suspended in PBS(-) [the same as Dullbecco's PBS but  $\text{CaCl}_2$  and  $\text{MgCl}_2$  are removed] to adjust  $1 \times 10^7$  cells/ml. 500  $\mu\text{l}$  of this suspension was injected to a cuvette, 10  $\mu\text{g}$  of said plasmid DNA was added, and the mixture was kept standing on ice for 5 minutes. This liquid was pulsed at 125  $\mu\text{F}$  and 300 V, using a gene pulsar (produced by Bio-Rad Laboratories), and then again kept standing on ice for 10 minutes. This liquid was transferred to 10 ml of 5% FCS/ASF104 medium and cultured at  $37^\circ\text{C}$  in the presence of 5% carbon dioxide. Forty-eight hours later the culture was transferred to a selection medium (5% FCS/ASF104 medium containing 200  $\text{fg/ml}$  G418) and cultured on a 24-well plate for 2 weeks. A number of colonies emerged, each of which was transferred to an ASF104 medium containing 200  $\mu\text{g/ml}$  G418 and cultured, followed by Western blot analysis of the culture supernatant using the human cathepsin L antiserum prepared in Experimental Example 3. In response to the antiserum, unique bands appeared having molecular weights of about 40,000 to 30,000 and lower molecular weights; they were identified as a precursor of human cathepsin L and processing products thereof, as estimated from their molecular weights. The culture supernatant was assayed for cathepsin L enzyme activity, in accordance with the method of A.J. Barrett and H. Kirschke [Methods in Enzymology, 80,535(1981)]; human cathepsin L activity was detected.

These findings confirm that transformed mouse myeloma cells expressing cathepsin L were obtained; these were designated as mouse myeloma Sp-HCL26.

Experimental Example 7: Purification of human cathepsin L

The strain obtained in Experimental Example 6, showing high expression of cathepsin L, (mouse myeloma Sp-HCL26, transformed with the plasmid pTBN-HCLneo, has been deposited under accession number IFO 50371 at the Institute for Fermentation, Osaka (IFO) since June 16, 1992 and under accession number FERM BP 3902 at the Fermentation Research Institute (FRI), Agency of Industrial Science and Technology since June 24, 1992), was cultured in 20 ml of an ASF104 medium supplemented with 10% FCS and 200  $\mu\text{g/ml}$  G418, after which it was transferred to 50 ml of a serum-free selection medium (ASF104 medium supplemented with 200  $\mu\text{g/ml}$  G418) and cultured for 5 days. After the culture supernatant was applied to a column of CM-Sephadex C-50 ( $25 \times 4.4$  cm), the column was washed with buffer A (20 mM sodium acetate, 1 mM EDTA, pH 5.5), followed by elution on a sodium chloride (NaCl) density gradient from 0 to 1 M, to elute human cathepsin L near a NaCl concentration of about 0.4 M. This fraction was applied to a Mono S column (HR5/5) of an FPLC system (produced by Pharmacia), followed by column washing and human cathepsin L elution in the same manner as above. The human cathepsin L fraction, eluted near a NaCl concentration of about 0.36 M, was concentrated to yield a purified preparation.

Experimental Example 8: Determination of human cathepsin L inhibitory activity

The recombinant human cathepsin L purified in Experimental Example 7 was diluted with a diluent [0.1% Brij 35 (produced by Sigma Chemical Company)] to a concentration of 1  $\mu\text{g/ml}$ . To 1  $\mu\text{l}$  of this enzyme dilution, 46  $\mu\text{l}$  of the diluent, 2  $\mu\text{l}$  of 0.1 M DTT and 25  $\mu\text{l}$  of an activator/buffer (340 mM sodium acetate, 60 mM acetic acid, 4 mM disodium EDTA, pH 5.5) were added. To this mixture were added a 1  $\mu\text{l}$  sample, diluted to  $10^{-2}$  M with dimethyl sulfoxide (DMSO), and 25  $\mu\text{l}$  of 20  $\mu\text{M}$  Z-Phe-Arg-NMec (enzyme substrate solution), followed by incubation at  $30^\circ\text{C}$  for 10 minutes, after which 100  $\mu\text{l}$  of a reaction stopper (100 mM sodium monochloroacetate, 30 mM sodium acetate, 70 mM acetic acid, pH 4.3) was added. This

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reaction was carried out on a 96-well fluoroplate (produced by Labo Systems).

After the reaction was stopped, the fluorescence intensity of free aminomethylcoumarin was determined at a wavelength of 450 nm (excitation wavelength = 365 nm), using a fluorometer FCA (produced by Baxter). For a control, 1  $\mu$ l of sample-free DMSO was added instead; the fluorometric value obtained from this control reaction was taken as 100% activity. When the residual activity was not higher than 10%, the sample solution was further diluted and then assayed for residual activity in the same procedure as above to obtain the  $IC_{50}$  value. The results are given in Table 1.

10

15

20

25

30

35

40

45

50

55

Table 1

Compound (Example No.)	Cathepsin L Inhibitory Activity [IC <sub>50</sub> Value (M)]
101	$2.2 \times 10^{-9}$
102	$3.3 \times 10^{-9}$
103	$1.9 \times 10^{-9}$
107	$1.1 \times 10^{-8}$
108	$5.4 \times 10^{-9}$
109	$1.0 \times 10^{-8}$
110	$1.6 \times 10^{-8}$
111	$1.4 \times 10^{-8}$
112	$3.8 \times 10^{-7}$
114	$6.1 \times 10^{-9}$
115	$4.8 \times 10^{-8}$
117	$2.0 \times 10^{-9}$
118	$2.2 \times 10^{-7}$
122	$3.2 \times 10^{-8}$
124	$5.3 \times 10^{-9}$
128	$1.9 \times 10^{-8}$
129	$8.5 \times 10^{-8}$
132	$9.9 \times 10^{-10}$
135	$1.0 \times 10^{-9}$
143	$1.7 \times 10^{-9}$
144	$2.4 \times 10^{-9}$
150	$6.1 \times 10^{-9}$
153	$3.1 \times 10^{-9}$
154	$9.5 \times 10^{-10}$
158	$1.4 \times 10^{-9}$
167	$4.3 \times 10^{-8}$
168	$2.6 \times 10^{-8}$
175	$1.9 \times 10^{-8}$
188	$3.7 \times 10^{-9}$
190	$5.5 \times 10^{-8}$
191	$4.7 \times 10^{-9}$
192	$4.2 \times 10^{-9}$
193	$3.9 \times 10^{-9}$

## Experimental Example 9: Bone resorption suppressing action

Bone resorption was measured by the method of Raisz [Journal of Clinical Investigation 44, 103-116- (1965)]. Specifically, one Sprague-Dawley rat, at 18 days of gestation, was given 50  $\mu$ Ci of  $^{45}\text{Ca}$  (calcium

isotope, in  $\text{CaCl}_2$  solution) by subcutaneous injection. On the following day, the animal was laparotomized and fetal rats aseptically removed. Both forearm bones (radius and ulna) were cut out from the body of each fetus under an anatomical microscope, and connective tissue and cartilages were removed to the maximum possible extent, to prepare bone culture samples. Each bone fragment was pre-cultured at  $37^\circ\text{C}$  for 24 hours in 0.6 ml of BGJb medium (Fitton-Jackson modification, GIBCO Laboratories, United States) prepared by adding bovine serum albumin (final concentration 2 mg/ml), after which it was transferred to the same medium as above but containing each compound (final concentration 10  $\mu\text{g/ml}$  or 10  $\mu\text{M}$ ) and cultured for two more days.  $^{45}\text{Ca}$  radioactivity in the medium and  $^{45}\text{Ca}$  radioactivity in the bone were then measured, and the percent ratio of  $^{45}\text{Ca}$  released from the bone to the medium was calculated using the following equation:

$$\text{Percent ratio of } ^{45}\text{Ca} \text{ released from bone to medium} = \frac{[(^{45}\text{Ca} \text{ count in the medium})]}{[(^{45}\text{Ca} \text{ count in the medium}) + (^{45}\text{Ca} \text{ count in the bone})]} \times 100$$

For control, bone fractions from fetuses of the same litter were cultured for two days in the absence of the test compound. The mean  $\pm$  standard deviation for the values from five bone fragments in each group were calculated, and their percent ratios to the control were calculated. The results are given in Table 2.

Table 2

Compound (Example No.)	Concentration of Compound	Bone Resorption Inhibitory Activity [ <sup>45</sup> Ca Release Rate (Percent to Control)]
3	10µg/ml	49
26	10µM	79
38	10µM	76
59	10µM	67
84	10µM	74
103	10µg/ml	49
108	10µg/ml	42
109	10µg/ml	38
110	10µg/ml	46
111	10µg/ml	32
112	10µg/ml	43
122	10µM	73
124	10µM	79
128	10µM	73
132	10µM	74
134	10µM	66
135	10µM	45
144	10µM	60
153	10µM	74
157	10µM	72
158	10µM	65

## Examples

### Reference Example 1

A mixture of N-benzyloxycarbonyl-(L)-isoleucyl-(L)-tryptophan methyl ester (11.3g), palladium-carbon (5%, 50% wet, 3.0g) and THF (50ml) was subjected to catalytic hydrogenation at room temperature and atmospheric pressure. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to yield an oily substance. The oil was dissolved in N,N-dimethylformamide (50ml), and 1-naphthalenesulfonyl chloride (5.8g) and 4-(N,N-dimethylamino)pyridine (DMAP) (3.2g) were added to the

ice-cooling mixture. After stirring at 0 °C for 3 hours, the reaction mixture was concentrated under reduced pressure. The residue was suspended in ethyl acetate and the mixture was successively washed with 10% aqueous citric acid solution, water, saturated aqueous sodium hydrogen carbonate and brine, and dried (MgSO<sub>4</sub>). The organic solvent was evaporated off to yield N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophan methyl ester (9.8g, 77%) as crystals. Melting point: 172-174 °C

#### Reference Example 2

To an ice-cooled mixture of N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophan methyl ester (6.9g) and THF (40ml)-methanol (20ml) was added dropwise a solution of KOH (1.5g) in water (10ml). After stirring at 0 °C for 20 hours, the reaction mixture was acidified with 1N HCl (35ml) with ice-cooling, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried (MgSO<sub>4</sub>). The organic solvent was evaporated off to yield N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophan (6.6g, 98%) as crystals. Melting point: 167-168 °C

#### Reference Example 3

To a stirred solution of p-nitrobenzyl chloride (15g) and diethyl benzylmalonate (22g) in N,N-dimethyl-formamide (150ml) was added NaH (60% in oil, 3.8g). After stirring at room temperature for 2 days, the reaction mixture was concentrated under reduced pressure and the residue was suspended in ethyl acetate. The ethyl acetate layer was washed with aqueous citric acid solution, water, saturated aqueous sodium hydrogen carbonate solution and brine, and dried (MgSO<sub>4</sub>). The organic solvent was evaporated off and the residual oil was purified by column chromatography on silica gel. Elution with ethyl acetate-hexane (1:6, v/v) gave diethyl benzyl-4-nitrobenzylmalonate (24g, 71%) as crystals. Melting point: 70-71 °C

#### Reference Example 4

A mixture of diethyl benzyl-4-nitrobenzylmalonate (24g), KOH (14g) and water (100ml)-ethanol (150ml) was stirred at 90-100 °C for 7 hours. The reaction mixture was concentrated under reduced pressure and the residue was acidified with 1N HCl and extracted with ethylacetate. The ethyl acetate layer was washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was dissolved in pyridine (100ml) and the solution was stirred at 90 °C for 16 hours. The organic solvent was evaporated off and the residue was acidified with 1N HCl and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel. Elution with ethyl acetate-hexane (1:3, v/v) gave 2-benzyl-3-(p-nitrophenyl)-propionic acid (10.5g, 59%) as crystals. Melting point: 104-105 °C

#### Reference Example 5

2-Benzyl-3-(p-nitrophenyl)propionic acid was converted to N-[2-benzyl-3-(p-nitrophenyl)propionyl]-(L)-tryptophanol by the method described for Example 1. Amorphous solid.  $[\alpha]_D^{25} -12.5^\circ$  (c 0.78, CHCl<sub>3</sub>). NMR ( $\delta$  ppm in CDCl<sub>3</sub>): 2.3-3.1 (7H,m), 3.2-3.4 (2H,m), 3.9-4.1 (1H,m), 5.20 & 5.34 (1H, each d,J=7.2Hz), 6.58 & 6.62 (1H, each d,J=2.0Hz), 7.0-7.4 (11H,m), 7.92 & 8.02 (2H, each d,J=8.2Hz), 8.04 (1H, broad s)

Elemental analysis (for C <sub>27</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> • 1/4H <sub>2</sub> O)			
Calculated	C, 70.19;	H, 6.00;	N, 9.09
Found	C, 70.00;	H, 6.25;	N, 8.88

#### Reference Example 6

A mixture of diethyl 4-aminobenzylphosphonate (10g) and diethyl benzylmalonate (24g) was stirred at 160 °C for 24 hours. After cooling, the reaction mixture was purified by column chromatography on silica gel. Elution with chloroform-methanol (100:1, v/v) gave ethyl 2-(p-diethoxyphosphorylmethylphenylaminocarbonyl)-3-phenylpropionate (8.3g, 45%) as crystals. Recrystallization from ethyl acetate-hexane gave colorless crystals having melting point of 115 to 116 °C

## Reference Example 7

To an ice-cooled and stirred solution of ethyl 2-(p-diethoxyphosphorylmethylphenylaminocarbonyl)-3-phenylpropionate (6.0g) in THF (30ml)-ethanol (10ml) was added dropwise a solution of KOH (0.9g) in water (10ml). After stirring at 4°C-room temperature for 15 hours, the reaction mixture was acidified with 1N HCl, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried (MgSO<sub>4</sub>). The organic solvent was evaporated off to yield 2-(p-diethoxyphosphorylmethylphenylaminocarbonyl)-3-phenylpropionic acid (5.3g, 94%) as crystals. Recrystallization from ethyl acetate-hexane gave pale yellow needles having melting point of 160 to 161 °C

## Reference Example 8

To an ice-cooled and stirred solution of N-(2-ethoxycarbonyl-3-phenylpropionyl)-(L)-tryptophanol (15g) in THF (40ml)-methanol (30ml) was added dropwise a solution of KOH (2.5g) in water (10ml). After stirring at 4°C-room temperature for 20 hours, the reaction mixture was acidified with 1N HCl, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried (MgSO<sub>4</sub>). The organic solvent was evaporated off to yield N-(2-carboxy-3-phenylpropionyl)-(L)-tryptophanol (13.5g, 97%) as crystals. Recrystallization from ethyl acetate-hexane gave pale yellow crystals having melting point of 130 to 131 °C

## Example 1

A mixture of N-benzyloxycarbonyl-(L)-tryptophanol (0.974 g) in methanol (10 ml), palladium-carbon (10%, 0.195 g) was subjected to catalytic hydrogenation at room temperature under 1 atmospheric pressure. After the palladium-carbon was filtered off, the filtrate was concentrated under reduced pressure to yield an oily substance. This oily substance and N-benzyloxycarbonyl-(L)-phenylalanine (0.90 g) were dissolved in tetrahydrofuran (THF) (20 ml), and 1-hydroxybenzotriazole (HOBt) (0.506 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD•HCl) (0.69 g) were added at 0 °C. After stirring at room temperature for 21 hours, the reaction mixture was poured over ethyl acetate. The ethyl acetate layer was washed by sequential additions of a 10% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution and saturated saline and then dried (MgSO<sub>4</sub>). After the solvent was distilled off, the oily residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (2:1) to yield N-benzyloxycarbonyl-(L)-phenylalanyl-(L)-tryptophanol (0.878 g, 62%).

Melting point: 154-156 °C

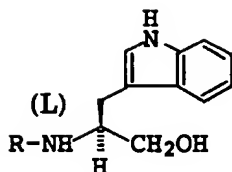
[ $\alpha$ ]<sub>D</sub> = -24.2° (c 0.24, DMSO)

Elemental analysis (for C <sub>28</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> • 0.2H <sub>2</sub> O)			
Calculated	C, 70.78;	H, 6.24;	N, 8.84
Found	C, 70.86;	H, 6.25;	N, 8.70

## Examples 2 through 11

The same procedure as in Example 1 was followed to yield the compounds listed in Table 3.

Table 3



Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
2	tBuOCO-Ile-	105-108	Ethyl acetate-hexane	-31.5° (c 0.375, CHCl <sub>3</sub> )
3	1-Nap-SO <sub>2</sub> -Ile-	150-151	CH <sub>2</sub> Cl <sub>2</sub> -ether	-77.7° (c 0.57, CHCl <sub>3</sub> )
4	4-Tol-SO <sub>2</sub> -Phe-	159-160	Ethyl acetate-hexane	-6.3° (c 0.485, DMSO)
5	1-Nap-SO <sub>2</sub> -Gly-	Note <sup>1)</sup> —	—	-9.2° (c 0.50, CHCl <sub>3</sub> )
6	PhCH <sub>2</sub> OCO-Ile-Ile-	184-185	Tetrahydrofuran-hexane	-40.0° (c 0.145, DMSO)
7	PhCH <sub>2</sub> OCO-Ile-	184-185	Ethyl acetate-hexane	-40.0°C (c 0.50, DMSO)
8	tBuOCO-Ile-Ile-	Note <sup>2)</sup> —	—	-19.4° (c 0.17, DMSO)
9	1-Nap-SO <sub>2</sub> -Ile-Ile-	170-172	Ethyl ether	-37.5° (c 0.2, DMSO)
10	CH <sub>3</sub> OCO(CH <sub>2</sub> ) <sub>2</sub> CO-Ile-Ile-	213-214	Tetrahydrofuran-hexane	
11	1-Ada-(CH <sub>2</sub> ) <sub>2</sub> OCO-Ile-Ile-	Note <sup>3)</sup> —	—	

Ile: (L)-isoleucine, Phe: (L)-phenylalanine, Gly: glycine, tBu: tert-butyl, 1-Nap: 1-naphthyl, 4-Tol: 4-tolyl, Ph: phenyl, 1-Ada: adamantan-1-yl

Note 1) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 2.69 (2H, dd, J = 4 & 6 Hz), 3.35 (2H, d, J = 6 Hz), 3.25-3.49 (3H, m), 4.06-4.14 (1H, m), 6.32 (1H, t, J = 6 Hz), 6.71 (1H, d, J



= 8.0 Hz), 6.92 (1H, d, J = 2 Hz), 7.04 (1H, dt, J = 1 & 7 Hz), 7.13 (1H, dt, J = 1 & 7 Hz), 7.26 (1H, d, J = 8 Hz), 7.39 (1H, t, J = 8 Hz), 7.49 (1H, d, J = 10 Hz), 7.50 (2H, dd, J = 7 & 9 Hz), 7.86 (1H, dd, J = 3 & 7 Hz), 7.96 (1H, d, J = 8 Hz), 8.11 (1H, dd, J = 1 & 7 Hz), 8.27 (1H, d, J = 2 Hz), 8.50 (1H, dd, J = 3 & 6 Hz)

Note 2) Amorphous solid

NMR ( $\delta$  ppm in  $d_6$ -DMSO): 0.76-0.82 (12H, m), 1.00-1.18 (2H, m), 1.28-1.47 (2H, m), 1.37 (9H, s), 1.60-1.75 (2H, m), 2.67-2.96 (2H, m), 3.31-3.36 (2H, m), 3.77-3.85 (1H, m), 3.93-4.04 (1H, m), 4.13-4.22 (1H, m), 4.65 (1H, t, J = 5.2 Hz), 6.87-7.09 (4H, m), 7.32 (1H, d, J = 7.4 Hz), 7.59-7.78 (3H, m), 10.75 (1H, br s). SI-MS m/z: 517 (MH<sup>+</sup>).

Note 3) Amorphous solid

NMR ( $\delta$  ppm in  $d_6$ -DMSO): 0.74-0.83 (12H, m), 0.98-1.16 (2H, m), 1.28-1.90 (21H, m), 2.68-2.95 (2H, m), 3.25-3.42 (2H, m), 3.83-4.21 (5H, m), 4.65 (1H, t, J = 5.6 Hz), 6.92-7.16 (4H, m), 7.31 (1H, d, J = 7.4 Hz), 7.62 (1H, d, J = 7.0 Hz), 7.69-7.75 (2H, m), 10.74 (1H, br s). SI-MS m/z: 623 (MH<sup>+</sup>).

Example 12

The same procedure as in Example 1 was followed to yield N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-isoleucyl-(DL)-(1-naphthyl)alaninol, which was recrystallized from ethyl acetate. Melting point: 198-200 °C

Example 13

A mixture of N-benzyloxycarbonyl-(L)-isoleucyl-(L)-tryptophanol (2.14 g), palladium-carbon (5%, 50% wet, 1.0 g) and methanol-THF (5:1, 30 ml) was subjected to catalytic hydrogenation at room temperature and atmospheric pressure. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to yield an oily substance. The oil and valproic acid (0.71 g) were dissolved in N,N-dimethylformamide (20 ml), and 1-hydroxybenzotriazole (HOBt) (0.82 g) and a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (1.13 g) in dichloromethane (20 ml) were added thereto at 0 °C. After stirring at 0 °C for 1 hour and at room temperature for 15 hours, the reaction mixture was concentrated under reduced pressure and the residue was suspended in ethyl acetate (120 ml). The mixture was successively washed with 10% aqueous citric acid solution, water, saturated aqueous sodium hydrogen carbonate and brine, and dried (MgSO<sub>4</sub>). The organic solvent was evaporated off to yield N-valproyl-(L)-isoleucyl-(L)-tryptophanol (1.78 g, 84.8%) as crystals. Recrystallization from ethyl acetate-hexane gave colorless needles.

Melting point: 190-191 °C

$[\alpha]_D = -60.8^\circ$  (c 0.50, CH<sub>3</sub>OH)

Elemental analysis (for C <sub>25</sub> H <sub>33</sub> N <sub>3</sub> O <sub>3</sub> )			
Calculated	C, 69.90;	H, 9.15;	N, 9.78
Found	C, 69.69;	H, 9.14;	N, 9.50

## Example 14

A mixture of N-benzyloxycarbonyl-(L)-tryptophan (1.0 g) in ethanol hydrogenation (20 ml)-dioxane (40 ml), palladium-carbon (5%, 0.5 g) was subjected to catalytic hydrogenation at room temperature under 1  
 5 atmospheric pressure. After the palladium-carbon was filtered off, the filtrate was concentrated under reduced pressure to yield an oily substance. This oily substance was dissolved in N,N-dimethylformamide (10 ml), and 1-naphthalenesulfonyl chloride (0.77 g) was added and then triethylamine (0.39 g) was added at 0°C. After overnight stirring at room temperature, the reaction mixture was poured over water and extracted with ether. The ether layer was washed by sequential additions of a 10% aqueous citric acid  
 10 solution, a saturated aqueous sodium hydrogen carbonate solution and saturated saline and then dried (MgSO<sub>4</sub>). After the solvent was distilled off, the oily residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:1) to yield a powder of N-(1-naphthylsulfonyl)-(L)-tryptophan (0.8 g, 68%).

Melting point: 85-87°C

15  $[\alpha]_D = -104.9^\circ$  (c 0.5, CHCl<sub>3</sub>)

## Example 15

A solution of N-benzyloxycarbonyl-(DL)- $\alpha$ -naphthylalanine (6.0 g) in ethyl acetate (200 ml) was treated  
 20 with a solution of diazomethane in ether to yield N-benzyloxycarbonyl-(DL)- $\alpha$ -naphthylalanine methyl ester as an oily substance. This oily substance was dissolved in ethanol (60 ml)-tetrahydrofuran (THF) (40 ml), and sodium borohydride (1.3 g) and lithium chloride (LiCl) (1.5 g) were added under an argon stream. After stirring at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure, and the residue poured over ethyl acetate. The ethyl acetate layer was washed by sequential additions of a  
 25 saturated aqueous sodium hydrogen carbonate solution and saturated saline and then dried (MgSO<sub>4</sub>). The solvent was distilled off to yield N-benzyloxycarbonyl-(DL)- $\alpha$ -naphthylalaninol (5.3 g, 91%) as a colorless solid.

<sup>1</sup>H-NMR ( $\delta$  ppm in CDCl<sub>3</sub>): 3.29 (1H,dd,J=8.2&12.8Hz), 3.42 (1H dd,J=7.2&12.8Hz), 3.5-3.8 (2H,m), 4.0-4.2 (1H,m), 5.11 (2H,s), 7.3-7.9 (12H,m), 8.21 (1H,d,J=7.2Hz)

30

## Example 16

A mixture of N-benzyloxycarbonyl-(L)-isoleucyl-(L)-tryptophan (55 g), palladium-carbon (5%, 50% wet, 30 g) and ethanol (50 ml)-THF (300 ml) was subjected to catalytic hydrogenation at room temperature and  
 35 atmospheric pressure. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to yield an oily substance. The oil was dissolved in N,N-dimethylformamide (300 ml), and 1-naphthalenesulfonyl chloride (30 g) and 4-(N,N-dimethylamino)pyridine (DMAP) (17 g) were added to the ice-cooling mixture. After stirring at 0°C for 2 hours, the reaction mixture was concentrated under reduced pressure. The residue was suspended in ethyl acetate and the mixture was successively washed with 10%  
 40 aqueous citric acid solution, water, saturated aqueous sodium hydrogen carbonate and brine, and dried (MgSO<sub>4</sub>). The organic solvent was evaporated off and the residual oil was purified by column chromatography on silica gel. Elution with ethyl acetate-hexane (3:2,v/v) gave N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophan (51 g, 82%) as crystals.

## 45 Example 17

To a solution, being ice cooled, of N-tert-butoxycarbonyl-(L)-isoleucyl-(L)-tryptophan (1.0 g) in chloroform (10 ml), trifluoroacetic acid (5%, 0.5 g) was added, followed by stirring at the same temperature for 4 hours. After the reaction mixture was concentrated under reduced pressure, ethyl acetate was added to the  
 50 residue. The ethyl acetate layer was washed with water and dried (MgSO<sub>4</sub>), and the solvent was distilled off to yield (L)-isoleucyl-(L)-tryptophan as an oily substance. This oily substance was dissolved in chloroform (20 ml), and p-toluenesulfonyl chloride (0.52 g) was added and then triethylamine (1.4 ml) was added at 0°C. After stirring at room temperature for 2 days, the reaction mixture was poured over water and extracted with chloroform. After the chloroform layer was dried (MgSO<sub>4</sub>), the solvent was distilled off, and  
 55 the oily residue was recrystallized from ethyl acetate to yield N-(p-toluenesulfonyl)-(L)-isoleucyl-(L)-tryptophan (0.32 g, 28%).

Melting point: 217-219°C

$[\alpha]_D = -32.7^\circ$  (c 0.695, CH<sub>3</sub>OH)

## Example 18

A mixture of N-benzyloxycarbonyl-(L)-isoleucyl-(L)-tryptophanol (0.7 g) in ethanol (30 ml)-tetrahydrofuran (20 ml), palladium-carbon (5%, 0.5 g) was subjected catalytic hydrogenation at room temperature under 1 atmospheric pressure. After the palladium-carbon was filtered off, the filtrate was concentrated under reduced pressure to yield an oily substance. This oily substance was dissolved in dichloromethane (15 ml)-tetrahydrofuran (5 ml), and m-methylphenyl isocyanate (0.225 g) was added at 4°C. After stirring at room temperature for 1.5 hours, the reaction mixture was poured over chloroform-methanol. After the insoluble substances were filtered off, the filtrate was concentrated under reduced pressure, and the residual solid was recrystallized from dichloromethane-methanol-hexane to yield N-(3-methylphenylcarbamoyl)-(L)-isoleucyl-(L)-tryptophanol (0.43 g, 61%).  
Melting point: 185-186°C

15

Elemental analysis (for C <sub>25</sub> H <sub>32</sub> N <sub>4</sub> O <sub>3</sub> )			
Calculated	C, 68.78;	H, 7.39;	N, 12.83
Found	C, 68.35;	H, 7.41;	N, 12.91

## 20 Example 19

The same procedure as in Example 18 was followed to yield N-benzylcarbamoyl-(L)-isoleucyl-(L)-tryptophanol.  
Melting point: 132-133°C  
[α]<sub>D</sub> = -42.9° (c 0.34, DMSO)

## Example 20

The same procedure as in Example 18 was followed to yield N-[(2-cyclohexylethyl)carbamoyl]-(L)-isoleucyl-(L)-tryptophanol.  
Melting point: 182-184°C  
[α]<sub>D</sub> = -27.7° (c 0.37, DMSO)

## 35 Example 21

The same procedure as in Example 18 was followed to yield N-isopropylcarbamoyl-(L)-isoleucyl-(L)-tryptophanol.  
Melting point: 211-213°C

## 40 Example 22

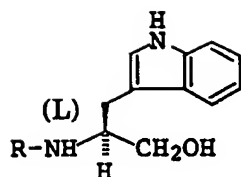
The same procedure as in Example 18 was followed to yield N-[(2-trifluoromethylphenyl)carbamoyl]-(L)-isoleucyl-(L)-tryptophanol.  
Melting point: 232-234°C

## 45 Examples 23 through 53

The same procedure as in Examples 1, 16 and 18 was followed to yield the compounds listed in Table 4.

55

Table 4



15

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation $[\alpha]_D$ (c, solvent)	Procedure followed (Example No.)
23	PhCH <sub>2</sub> OCO-Gly-	87-88	Ethyl acetate-ether	-15.0° (0.50, CHCl <sub>3</sub> )	1
24	tBuOCO-Phe-	150-151	Ethyl acetate-hexane	-20.2° (0.96, CHCl <sub>3</sub> )	1
25	1-Nap-SO <sub>2</sub> -Phe-	- <sup>1)</sup>		-113.3° (0.86, CHCl <sub>3</sub> )	16
26	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	120-121	Ethyl acetate-hexane	-13.9° (0.62, CHCl <sub>3</sub> )	1
27	PhCH <sub>2</sub> CH <sub>2</sub> CO-	134-135	Ethyl acetate-hexane	-14.5° (0.54, CHCl <sub>3</sub> )	1
28	1-Nap-SO <sub>2</sub> -Ala-	- <sup>2)</sup>		-77.5° (0.50, CHCl <sub>3</sub> )	16
29	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Ala-	144-145	Ethyl acetate-hexane	-64.7° (0.50, CH <sub>3</sub> OH)	13
30	PhCH <sub>2</sub> OCO-Trp-	105-106	Ethyl acetate-ether	-43.4° (1.05, DMSO)	1
31	tBuOCO-Trp-	120-122	Ethyl acetate-ether	-39.7° (0.62, DMSO)	1

40

Table 4 (continued)

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)	Procedure followed (Example No.)
32	PhCO-Phe-	165-167	DMF-H <sub>2</sub> O	-46.3° (0.745, DMSO)	1
33	(PhS)(C <sub>3</sub> H <sub>7</sub> )CHCO-	141-142	Ethyl acetate	+66.6° (0.55, CHCl <sub>3</sub> )	1
34	PhCH <sub>2</sub> NHCS-Ile-	- <sup>3)</sup>	Ethyl acetate-ether	-40.4° (0.255, DMSO)	18
35	1-Nap-NHCO-Ile-	217-218	Ethyl acetate-methanol	-5.6° (0.325, DMSO)	18
36	PhCH <sub>2</sub> OCO-Val-	163-164	Ethyl acetate-hexane	-43.3° (0.50, CH <sub>3</sub> OH)	1
37	1-Nap-SO <sub>2</sub> -Val-	- <sup>4)</sup>		-28.8° (0.50, CH <sub>3</sub> OH)	16
38	PhCO-Val-	173-174	Ethyl acetate-hexane	-35.8° (0.50, CH <sub>3</sub> OH)	1
39	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Val-	187-188	Ethyl acetate-hexane	-63.8° (0.50, CH <sub>3</sub> OH)	13
40	(2-benzimidazolyl-S)(C <sub>3</sub> H <sub>7</sub> )CHCO-	165-167	Ethyl acetate-hexane	-52.1° (0.53, CH <sub>3</sub> OH)	1
41	PhNHCS-Ile-	- <sup>5)</sup>	-	-26.9° (0.295, CHCl <sub>3</sub> )	18
42	1-Nap-NHCS-Ile-	- <sup>6)</sup>	-	-11.7° (0.43, CHCl <sub>3</sub> )	16
43	PhCO-Gly	149-150	Ethyl acetate-hexane	-16.3° (0.50, CH <sub>3</sub> OH)	1
44	PhCH <sub>2</sub> OCO-Ala-	158-159	Ethyl acetate-hexane	-40.1° (0.50, CH <sub>3</sub> OH)	1
45	PhCH <sub>2</sub> OCO-Leu-	103-104	Ethyl acetate-hexane	-46.1° (0.50, CH <sub>3</sub> OH)	1
46	1-Nap-SO <sub>2</sub> -Leu-	- <sup>7)</sup>	-	-100.7° (0.50, CHCl <sub>3</sub> )	16
47	PhCO-Leu-	200-201	Ethyl acetate	-39.5° (0.50, CH <sub>3</sub> OH)	1

Table 4 (continued)

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation $[\alpha]_D$ (c, solvent)	Procedure followed (Example No.)
48	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Leu-	149-150	Ethyl acetate-hexane	-64.8° (0.50, CH <sub>3</sub> OH)	13
49	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Gly-	177-178	Ethyl acetate-hexane	-13.2° (0.50, CH <sub>3</sub> OH)	13
50	PhCO-Ile-	142-143	Ethyl acetate-hexane	-27.2° (0.26, CHCl <sub>3</sub> )	1
51	Ph(CH <sub>2</sub> ) <sub>3</sub> CO-	99-100	Ethyl acetate-hexane	-15.5° (0.435, CHCl <sub>3</sub> )	1
52	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Phe-	191-192	Ethyl acetate-hexane	-34.3° (0.50, CH <sub>3</sub> OH)	13
53	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-	153-154	CHCl <sub>3</sub> -ethanol-isopropyl ether	-19.8° (0.50, CHCl <sub>3</sub> )	1

DMSO: dimethyl sulfoxide, DMF: N, N-dimethylformamide, Ph: phenyl, 1-Nap: 1-naphthyl, tBu: tert. butyl

5 Ile: (L)-isoleucine, Leu: (L)-leucine, Ala: (L)-alanine, Gly: glycine, Val: (L)-valine, Trp: (L)-tryptophan, Phe: (L)-phenylalanine,

Note 1) Amorphous solid

10 NMR (8 ppm in CDCl<sub>3</sub>): 2.45 (1H,m), 2.58-3.00 (4H,m), 3.50 (1H,m), 3.72 (1H,m), 4.19 (1H,m), 5.00 (1H,m), 6.48 (1H,m), 6.60-6.70 (2H,m), 7.06-7.59 (6H,m), 7.87-8.21 (5H,m).

Note 2) Amorphous solid

15 NMR (8 ppm in CDCl<sub>3</sub>): 0.93 (3H,d,J=7Hz), 2.69-2.80 (1H,m), 2.74 (1H,dd,J=7&4Hz), 2.90 (1H,dd,J=7&15Hz), 3.34-3.52 (2H,m), 3.64 (1H,quintet,J=7Hz), 4.10-4.14 (1H,m), 5.45 (1H,d,J=7Hz), 6.61 (1H,d,J=8Hz), 7.00 (1H,d,J=2Hz), 7.11 (1H,dt,J=1&8Hz), 7.20 (1H,dt,J=8Hz), 7.34 (1H,dd,J=1&7Hz), 7.47 (1H,dt,J=8&7Hz), 7.56 (2H,dd,J=1&8Hz), 7.58-7.68 (1H,m), 7.92-7.97 (1H,m), 8.06 (1H,d,J=8Hz), 8.20 (1H,dd,J=1&7Hz), 8.22 (1H,s), 8.53 (1H,dd,J=2&8Hz).

Note 3) Amorphous solid

30 NMR (8 ppm in CDCl<sub>3</sub>): 0.7-1.2 (7H,m), 1.3-1.6 (1H,m), 1.7-2.0 (1H,m), 2.3-2.5 (1H,m), 2.85 (2H,d,J=6.2Hz), 3.3-3.6 (2H,m), 3.9-4.1 (1H,m), 4.4-4.6 (1H,m), 4.71 (2H,broad d,J=8.4Hz), 6.63 (1H,broad d,J=8.0Hz), 7.00 (1H,d,J=1.8Hz), 7.1-7.4 (8H,m), 7.56 (1H,d,J=7.4Hz), 8.10 (1H,s).

Note 4) Amorphous solid

40 NMR (8 ppm in CDCl<sub>3</sub>): 0.50 (6H,t,J=7Hz), 1.92-2.03 (1H,m), 2.48-2.54 (1H,m), 2.62 (1H,dd,J=7&15Hz), 2.80 (1H,dd,J=7&15Hz), 3.39 (2H,dd,J=5&7Hz), 4.03-4.09 (1H,m), 5.40 (1H,d,J=7Hz), 6.32 (1H,d,J=8Hz), 6.98 (1H,d,J=2Hz), 7.12 (1H,dt,J=1&7Hz), 7.20 (1H,dt,J=1&7Hz), 7.34 (1H,d,J=7Hz), 7.47 (1H,dd,J=7&8Hz), 7.53 (1H,d,J=8Hz), 7.60 (1H,dd,J=1&8Hz), 7.68 (1H,ddd,J=2&7&8Hz), 7.92 (1H,dd,J=1&7Hz), 8.66 (1H,d,J=9Hz).

50 Note 5) Amorphous solid

55

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 0.7-1.1 (7H,m), 1.2-1.5 (1H,m), 1.8-2.0 (1H,m), 2.80 (1H,t, $\underline{J}$ =5.4Hz), 3.00 (2H,d, $\underline{J}$ =6.8Hz), 3.5-3.8 (2H,m), 4.2-4.4 (1H,m), 4.78 (1H,t, $\underline{J}$ =7.4Hz), 6.47 (1H,d, $\underline{J}$ =7.8Hz), 6.71 (1H,d, $\underline{J}$ =8.0Hz), 7.0-7.4 (9H,m), 7.61 (1H,d, $\underline{J}$ =7.4Hz), 8.23 (1H,broad s), 8.26 (1H,d, $\underline{J}$ =10.0Hz).

Note 6) Amorphous solid

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 0.6-0.9 (7H,m), 1.0-1.3 (1H,m), 1.6-1.9 (1H,m), 2.73 (1H,t, $\underline{J}$ =6.2Hz), 2.9-3.1 (2H,m), 3.5-3.8 (2H,m), 4.1-4.3 (1H,m), 4.74 (1H,t, $\underline{J}$ =7.8Hz), 6.17 (1H,d, $\underline{J}$ =8.0Hz), 6.36 (1H,d, $\underline{J}$ =7.8Hz), 7.0-8.0 (12H,m), 8.16 (1H, broad s), 8.22 (1H, broad s).

Note 7) Amorphous solid

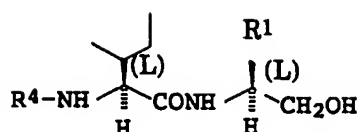
NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 0.16 (3H,d, $\underline{J}$ =6Hz), 0.56 (3H,d, $\underline{J}$ =6Hz), 1.04-1.19 (2H,m), 1.25-1.34 (1H,m), 2.68-2.79 (1H,m), 2.73 (1H,dd, $\underline{J}$ =7&15Hz), 2.89 (1H,dd, $\underline{J}$ =7&14Hz), 3.35-3.56 (3H,m), 4.07-4.18 (1H,m), 5.39 (1H,d, $\underline{J}$ =6Hz), 6.55 (1H,d, $\underline{J}$ =8Hz), 7.03 (1H,d, $\underline{J}$ =2Hz), 7.12 (1H,dt, $\underline{J}$ =1&7Hz), 7.21 (1H,dt, $\underline{J}$ =1&7Hz), 7.36 (1H,d, $\underline{J}$ =7Hz), 7.49 (1H,dd, $\underline{J}$ =7&8Hz), 7.58 (1H,d, $\underline{J}$ =7Hz), 7.59 (1H,dt, $\underline{J}$ =2&7Hz), 7.68 (1H,dt, $\underline{J}$ =2&7Hz), 7.95 (1H,dd, $\underline{J}$ =2&8Hz), 8.07 (1H,d, $\underline{J}$ =8Hz), 8.22 (1H,d, $\underline{J}$ =1Hz), 8.24 (1H,dd, $\underline{J}$ =1&7Hz), 8.61 (1H,d, $\underline{J}$ =8Hz).

Examples 54 through 68

The same procedure as in Example 1 and 16 was followed to yield the compounds listed in Table 5.



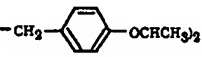
Table 5



10

Example No	R <sup>4</sup>	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)	Procedure followed (Example No.)
15 54	tBuOCO-		132-133	CH <sub>2</sub> Cl <sub>2</sub> -Ethyl acetate-hexane	-25.7° (0.34, DMSO)	1
20 55	PhCH <sub>2</sub> OCO-	-CH <sub>3</sub>	156-157	methanol-CH <sub>2</sub> Cl <sub>2</sub> -hexane	+2.3° (0.375, DMSO)	1
25 56	PhCH <sub>2</sub> OCO-	-CH <sub>2</sub> Ph	164-165	methanol-ethyl acetate	-38.0° (0.27, DMSO)	1
30 57	1-Nap-SO <sub>2</sub> -	-CH <sub>3</sub>	178-179	Ethyl acetate-hexane	+54.3° (0.38, DMSO)	16
35 58	1-Nap-SO <sub>2</sub> -	-CH <sub>2</sub> Ph	169-170	Ethyl acetate-hexane	-108.3° (0.65, CHCl <sub>3</sub> )	16
40 59	PhCH <sub>2</sub> OCO-		117-118	Ethyl acetate-hexane	-22.6° (0.295, CHCl <sub>3</sub> )	1
45 60	PhCH <sub>2</sub> OCO-		188-189	Ethyl acetate-hexane	-34.0° (0.355, DMSO)	1
50 61	PhCH <sub>2</sub> OCO-		174-175	Ethyl acetate-hexane	-34.0° (0.38, DMSO)	1
55 62	1-Nap-SO <sub>2</sub> -		204-205	Ethyl acetate-hexane	-9.3° (0.36, DMSO)	16

Table 5 (continued)

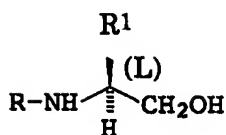
Example No	R <sup>4</sup>	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)	Procedure followed (Example No.)
63	1-Nap-SO <sub>2</sub> -		130-131	Ethyl acetate-hexane	-92.3° (0.34. CHCl <sub>3</sub> )	16
64	PhCH <sub>2</sub> OCO-	-CH(CH <sub>3</sub> ) <sub>2</sub>	149-150	Ethyl acetate	-36.7° (0.37. CHCl <sub>3</sub> )	1
65	PhCH <sub>2</sub> OCO-	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	151-153	Ethyl acetate-hexane	-34.1° (0.36. CHCl <sub>3</sub> )	1
66	1-Nap-SO <sub>2</sub> -	-CH(CH <sub>3</sub> ) <sub>2</sub>	159-160	Ethyl acetate	+8.0° (0.26. CHCl <sub>3</sub> )	16
67	1-Nap-SO <sub>2</sub> -	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	88-89	Ethyl acetate-hexane	+28.5° (0.265, DMSO)	16
68	PhCH <sub>2</sub> OCO-	H	160-161	Ethyl acetate-hexane	-4.9° (0.50. CHCl <sub>3</sub> )	1

DMSO: dimethyl sulfoxide, Ph: phenyl, 1-Nap: 1-naphthyl, tBu: tert. butyl

Examples 69 through 73

The same procedure as in Example 1 was followed to yield the compounds listed in Table 6.

Table 6



Example No	R	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
69	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH <sub>2</sub> Ph	115-116	CH <sub>2</sub> Cl <sub>2</sub> -hexane	-18.3° (0.56, CHCl <sub>3</sub> )
70	PhCH <sub>2</sub> OCO-Leu-Leu-	H	112-113	Ethyl acetate-hexane	-17.0° (0.305, DMSO)
71	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH <sub>2</sub> CH <sub>3</sub>	161-162	Ethyl acetate-methanol-hexane	-34.6° (0.54, CHCl <sub>3</sub> )
72	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH(CH <sub>3</sub> ) <sub>2</sub>	148-149	Ethyl acetate-hexane	-31.5° (0.50, CHCl <sub>3</sub> )
73	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH <sub>3</sub>	144-145	CH <sub>2</sub> Cl <sub>2</sub> -isopropyl ether-hexane	-17.9° (0.50, CHCl <sub>3</sub> )

Leu:(L) - leucine, Ph: phenyl

#### Example 74

The same procedure as in Example 1 was followed to yield N-benzyloxycarbonyl-(L)-isoleucyl-(D)-tryptophanol. m.p. 198-199° C (recrystallized from ethyl acetate-hexane).  
[α]<sub>D</sub> = +31.8° (c 0.945, DMSO)

#### Example 75

The same procedure as in Example 16 was followed to yield N-(1-naphthylsulfonyl)-(L)-isoleucyl-(D)-tryptophanol as an amorphous solid.

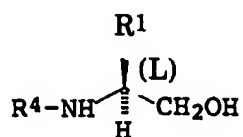
[α]<sub>D</sub> = -16.0° (c 0.34, CHCl<sub>3</sub>)

NMR(δ ppm in CDCl<sub>3</sub>): 0.4-0.9 (7H,m), 1.1-1.3 (1H,m), 1.5-1.7 (1H,m), 2.6-2.8 (1H,m), 2.74 (2H,d,J=7.0Hz), 3.2-3.4 (2H,m), 3.45 (1H,dd,J=6.0&8.2Hz), 3.9-4.2 (1H,m), 5.7-5.9 (1H,m), 6.1-6.3 (1H,m), 7.00 (1H,d,J=1.6Hz), 7.0-7.7 (7H,m), 7.90 (1H,d,J=8.0Hz), 7.99 (1H,d,J=8.4Hz), 8.20 (2H,d,J=7.2Hz), 8.67 (1H,d,J=8.2Hz)

#### Examples 76 through 97

The same procedure as in Examples 1 and 13 was followed to yield the compounds listed in Tables 7 and 8.

Table 7



Example No	R <sup>4</sup>	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)	Procedure followed (Example No.)
76	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-	PhCH <sub>2</sub> -	133-134	CH <sub>2</sub> Cl <sub>2</sub> -ether-isopropyl ether	-25.4° (0.5, CHCl <sub>3</sub> )	1
77	Ph(CH <sub>2</sub> ) <sub>3</sub> CO-	PhCH <sub>2</sub> -	113-114	AcOEt-ether-hexane	-22.8° (0.5, CHCl <sub>3</sub> )	1
78	PhCH <sub>2</sub> OCO-Leu-	H	126-127	AcOEt-hexane	+11.6° <sup>1)</sup> (0.41, DMSO)	1
79	1-Nap-SO <sub>2</sub> -Leu-Trp-	H	215-216	AcOEt	-15.4° (0.24, DMSO)	1

Leu:(L) - leucine, Trp:(L)-tryptophan, Ph: phenyl, 1-Nap:1-naphthyl, AcOEt: ethyl acetate  
 1) [α]<sub>Hg</sub>

Table 8

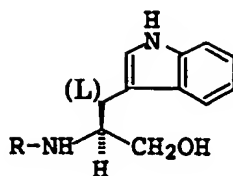


Table 8

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Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation $[\alpha]_D$ (c, solvent)	Procedure followed (Example No.)
15 80	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{CO-}$	114-115	AcOEt-hexane	-19.0° (0.5, CH <sub>3</sub> OH)	1
20 81	cyclohexyl-CO-	164-165	AcOEt-hexane	-20.8° (0.5, CH <sub>3</sub> OH)	1
25 82	Ph-CO-	129-130	AcOEt-hexane	-74.4° (0.5, CH <sub>3</sub> OH)	1
30 83	Ph(C <sub>2</sub> H <sub>5</sub> )CH-CO-	103-104	AcOEt-hexane	-22.4° (0.645, CHCl <sub>3</sub> )	1
35 84	(PhCH <sub>2</sub> )[(4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ]CH-CO-	- <sup>1)</sup>		-16.0° (0.53, CHCl <sub>3</sub> )	1
40 85	PhCH <sub>2</sub> CH <sub>2</sub> -CO-Val-	197-198	AcOEt-hexane	-60.7°C (0.50, CH <sub>3</sub> OH)	13
45 86	(PhCH <sub>2</sub> ) <sub>2</sub> CH-CO-Val-	157-158	AcOEt-hexane	-48.3 (0.50, CH <sub>3</sub> OH)	13
50 87	(PhCH <sub>2</sub> )[(2-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ]CH-CO-	98-100		-17.5° (0.53, CHCl <sub>3</sub> )	1
55 88	(PhCH <sub>2</sub> )[(4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ]CH-CO-	- <sup>2)</sup>		-24.8° (0.59, CHCl <sub>3</sub> )	1
89	[(4-PhCONH-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ](PhCH <sub>2</sub> )CH-CO-	173-174	AcOEt-hexane	-65.5° (0.535, CHCl <sub>3</sub> )	- <sup>6)</sup>

Table 8 (continued)

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation $[\alpha]_D$ (c, solvent)	Procedure followed (Example No.)
90	[(4-CH <sub>3</sub> CONH-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ](PhCH <sub>2</sub> )CH-CO-	114-115	AcOEt-hexane	-18.0° (0.475, CHCl <sub>3</sub> )	— 7)
91	[4-(4-Tol-SO <sub>2</sub> NH)-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> ](PhCH <sub>2</sub> )CH-CO-	150-151	AcOEt-hexane	-16.1° (0.815, DMSO)	— 8)
92	[[4-(C <sub>2</sub> H <sub>5</sub> O) <sub>2</sub> P(O)CH <sub>2</sub> ]-C <sub>6</sub> H <sub>4</sub> NHCO](PhCH <sub>2</sub> )CH-CO-	— 3)		-37.1° (0.52, CHCl <sub>3</sub> )	1
93	(C <sub>2</sub> H <sub>5</sub> OO)(PhCH <sub>2</sub> )CH-CO-	— 4)			1
94	[(PhCH <sub>2</sub> ) <sub>2</sub> N-CO](PhCH <sub>2</sub> )CHCO-	— 5)		-21.8° (0.405, CHCl <sub>3</sub> )	— 9)
95	(PhCH <sub>2</sub> NH-CO)-(PhCH <sub>2</sub> )CHCO-	187-188	AcOEt-hexane	-40.8° (0.83, DMSO)	— 10)
96	Ph <sub>2</sub> CH-CO-	207-209	AcOEt-hexane	-24.8° (0.345, DMSO)	1
97	(4-oxo-4H-1-benzopyran-2-yl)-CO-Ile-	164-165	ethanol-hexane	-54.8° (0.53, CH <sub>3</sub> OH)	13

Leu: (L)-leucine, Val: (L)-valine, Ph: phenyl, 4-Tol: 4-tolyl, AcOEt: ethyl acetate

Note 1) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 2.29&2.31 (3H,each s), 2.34-2.52 (1H,m), 2.60-3.08 (6H,m), 3.18-3.42 (2H,m), 3.93-4.11 (1H,m), 5.10-5.20 (1H,m), 6.42&6.50 (1H,each d,J=2.2Hz), 7.00-7.40 (13H,m), 7.89 (1H,broad).

Note 2) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 2.32-2.50 (1H,m), 2.60-3.07 (4H,m), 3.20-3.43 (2H,m), 3.75&3.78 (3H,each s), 3.92-4.15 (1H,m), 5.04-5.20 (1H,m), 6.31&6.43 (1H,each d,J=2.3Hz), 6.79 (2H,d,J=8.5Hz), 7.02-7.46 (9H,m), 7.87-8.00 (1H,broad).

## Note 3) Amorphous solid

NMR (8 ppm in CDCl<sub>3</sub>): 1.22 (3H,t,J=6.0Hz), 1.23 (3H,t,J=6.0Hz), 2.70-3.60  
 5 (10H,m), 3.90-4.10 (4H,m), 4.1-4.30 (1H,m), 6.70&6.83 (1H,each d,J=2.2Hz),  
 6.82&6.88 (1H,each d,J=8.0Hz), 7.0-7.4 (12H,m), 7.52&7.58 (1H,each d,J=7.4Hz),  
 8.37&8.46 (1H,each broad s), 9.29&9.31 (1H,each broad s).

## 10 Note 4) Oil

NMR (8 ppm in CDCl<sub>3</sub>): 1.10&1.12 (3H,each t,J=7.0Hz), 2.40-2.60 (1H,m),  
 2.91-3.22 (5H,m), 3.41-3.70 (2H,m), 3.98-4.30 (3H,m), 6.50-6.65 (1H,m), 6.89&6.98  
 15 (1H,each d,J=2.2Hz), 7.07-7.37 (8H,m), 7.57&7.65 (1H,each d,J=7.8Hz), 8.15  
 (1H,broad).

## Note 5) Amorphous solid

20 NMR (8 ppm in CDCl<sub>3</sub>): 2.6-3.4 (5H,m), 3.5-3.9(3H,m), 4.0-4.5 (4H,m), 6.65  
 (1H,d,J=6.8Hz), 6.71&6.75 (1H,each d,J=2.8Hz), 6.9-7.4 (18H,m), 7.68  
 (1H,d,J=7.0Hz), 8.07 (1H,broad s).

25 Note 6) Synthesized by catalytic reduction of N-[2-benzyl-3-(p-  
 nitrophenyl)propionyl]-(L)-tryptophanol (Reference Example 5) followed by  
 reaction with benzoyl chloride.

30 Note 7) Synthesized by catalytic reduction of N-[2-benzyl-3-(p-  
 nitrophenyl)propionyl]-(L)-tryptophanol (Reference Example 5) followed by  
 reaction with acetyl chloride.

35 Note 8) Synthesized by catalytic reduction of N-[2-benzyl-3-(p-  
 nitrophenyl)propionyl]-(L)-tryptophanol (Reference Example 5) followed by  
 reaction with tosyl chloride.

40 Note 9) Synthesized by reaction of N-(2-carboxy-3-phenylpropionyl)-(L)-  
 tryptophanol (Reference Example 8) with dibenzylamine using the method  
 described for Example 1.

45 Note 10) Synthesized by reaction of N-(2-carboxy-3-phenylpropionyl)-(L)-  
 tryptophanol (Reference Example 8) with benzylamine using the method described  
 for Example 1.

## 55 Example 98

To a solution of N-benzyloxycarbonyl-(L)-phenylalanyl-(L)-tryptophanol (0.60 g) and triethylamine (0.53 ml) in dimethyl sulfoxide (DMSO) (7 ml), a solution of pyridine-sulfur trioxide complex (pyridine·SO<sub>3</sub>) in

DMSO (7 ml) was added drop by drop. After stirring at room temperature for 1 hour, the reaction mixture was poured over ice water and extracted with ethyl ether (60 ml x 3). The ethyl ether layer was washed by sequential additions of a 10% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution and saturated saline and then dried ( $\text{MgSO}_4$ ). After the solvent was distilled off, the residue was solidified from THF-hexane-ethyl ether to yield N-benzyloxycarbonyl-(L)-phenylalanyl-(L)-tryptophanal (0.44 g, 74%) as a colorless powder.

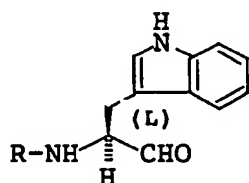
Melting point: 74-77 °C

$[\alpha]_D = +18.0^\circ$  (c 0.05,  $\text{CHCl}_3$ , 31 °C)

Examples 99 through 117

The same procedure as in Example 98 was followed to yield the compounds listed in Table 9.


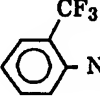
Table 9



Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation $[\alpha]_D$ (c, solvent)
99	3-Tol-NHCO-Ile-	202-204 (decomposed)	Methanol-dichloromethane-hexane	-20.8° (c 0.32, DMSO)
100	1-Nap-SO <sub>2</sub> -	160-161	Ethyl ether	-84.6° (c 0.5, $\text{CHCl}_3$ )
101	4-Tol-SO <sub>2</sub> -Ile-	199-201	—	-32.7° (c 0.51, $\text{CH}_3\text{OH}$ )
102	tBuOCO-Ile-	114-115	Isopropyl ether	+22.3° (c 0.775, $\text{CHCl}_3$ )



Table 9 (continued)

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
103	1-Nap-SO <sub>2</sub> -Ile-	145-146	Ethyl acetate-hexane	-54.4° (c 0.50, CHCl <sub>3</sub> )
104	PhCH <sub>2</sub> OCO-	105-106	Ethyl acetate-isopropyl ether	+49.0° (c 0.5, CHCl <sub>3</sub> )
105	4-Tol-SO <sub>2</sub> -Phe-	150-151	Ethyl acetate-ethyl ether	+15.4° (c 0.41, DMSO)
106	1-Nap-SO <sub>2</sub> -Gly-	135-136	—	-54.8° (c 0.50, CHCl <sub>3</sub> )
107	PhCH <sub>2</sub> OCO-Ile-	137-140	Ethyl acetate-hexane	+28.5° (c 0.4, MeOH)
108	PhCH <sub>2</sub> OCO-Ile-Ile-	Note <sup>1)</sup> —	—	+12.5° (c 0.12, CHCl <sub>3</sub> )
109	tBuOCO-Ile-Ile-	178-180	Tetrahydrofuran-dichloromethane-hexane	-36.5° (c 0.115, DMSO)
110	1-Nap-SO <sub>2</sub> -Ile-Ile-	159-160	Tetrahydrofuran-ethyl ether-hexane	-100.0° (c 0.125, CHCl <sub>3</sub> )
111	CH <sub>3</sub> OCO(CH <sub>2</sub> ) <sub>2</sub> CO-Ile-Ile-	Note <sup>2)</sup> —	—	—
112	1-Ada(CH <sub>2</sub> ) <sub>2</sub> OCO-Ile-Ile-	Note <sup>3)</sup> —	—	—
113	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-	135-136	Dichloromethane-ethyl ether	-86.8° (c 0.5, CHCl <sub>3</sub> )
114	Ph-CH <sub>2</sub> NHCO-Ile-	183-185	Chloroform-ethyl acetate	-16.9° (c 0.4, DMSO)
115	 -(CH <sub>2</sub> ) <sub>2</sub> NHCO-Ile-	168-169	Dichloromethane-ethyl acetate-hexane	-21.9° (c 0.325, DMSO)
116	(CH <sub>3</sub> ) <sub>2</sub> CHNHCO-Ile-	201-204 (decomp.)	Methanol-ethyl acetate	-15.9° (c 0.57, DMSO)
117	 -NHCO-Ile-	185-186 (decomp.)	Methanol-ethyl acetate	-18.7° (c 0.50, DMSO)

Ile: (L)-isoleucine, Phe: (L)-phenylalanine, Gly: glycine, tBu: tert-butyl, 1-Nap: 1-naphthyl, 3-Tol: 3-tolyl, 4-Tol: 4-tolyl, Ph: phenyl, 1-Ada: adamantan-1-yl

Note 1) Amorphous solid

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 0.84-0.90 (12H, m), 0.98-1.17 (2H, m), 1.36-1.51 (2H, m), 1.81-1.94 (2H, m), 3.27-3.33 (2H, m), 4.00 (1H, dd,  $J = 6.8$  &  $8.6$  Hz), 4.30 (1H, dd,  $J = 6.8$  &  $8.6$  Hz), 4.80 (1H, dd,  $J = 6.6$  &  $13.2$  Hz), 5.10 (2H, s), 5.28 (1H, d,  $J = 7.6$  Hz), 6.48 (1H, d,  $J = 8.6$  Hz), 6.62 (1H, d,  $J = 6.6$  Hz), 7.03-7.40, 7.55-7.60 (10H, m), 8.25 (1H, br s), 9.63 (1H, s). SI-MS  $m/z$ : 549 ( $\text{MH}^+$ ).

Note 2) Amorphous solid

NMR ( $\delta$  ppm in  $d_6$ -DMSO): 0.75-0.81 (12H, m), 0.98-1.13 (2H, m), 1.33-1.47 (2H, m), 1.66-1.75 (2H, m), 2.40-2.51 (4H, m), 2.93-3.25 (2H, m), 3.56 (3H, s), 4.16-4.26 (2H, m), 4.41 (1H, dd,  $J = 7.0$  &  $13.0$  Hz), 6.94-7.17 (3H, m), 7.34 (1H, d,  $J = 8.0$  Hz), 7.52 (1H, d,  $J = 7.6$  Hz), 7.79 (1H, d,  $J = 8.6$  Hz), 7.96 (1H, d,  $J = 8.8$  Hz), 8.42 (1H, d,  $J = 6.4$  Hz), 9.47 (1H, s), 10.86 (1H, br s). SI-MS  $m/z$ : 529 ( $\text{MH}^+$ ).

Note 3) Amorphous solid

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 0.85-0.91 (12H, m), 1.02-1.19 (2H, m), 1.36-1.96 (21H, m), 3.20-3.41 (2H, m), 3.93-4.02 (1H, m), 4.09-4.16 (2H, m), 4.32 (1H, dd,  $J = 6.8$  &  $8.4$  Hz), 4.82 (1H, dd,  $J = 7.0$  &  $13.4$  Hz), 5.12 (1H, d,  $J = 8.2$  Hz), 6.48 (1H, d,  $J = 8.6$  Hz), 6.63 (1H, d,  $J = 7.0$  Hz), 7.03-7.25 (3H, m), 7.37 (1H, d,  $J = 7.4$  Hz), 7.59 (1H, d,  $J = 7.2$  Hz), 8.28 (1H, br s), 9.63 (1H, s). SI-MS  $m/z$ : 621 ( $\text{MH}^+$ ).

Example 118

The same procedure as in Example 98 was followed to yield N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-isoleucyl-(DL)-(1-naphthyl)alaninal, which was recrystallized from ethyl acetate-tetrahydrofuran-hexane.

Melting point: 169-174 °C

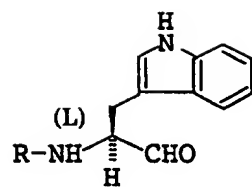
NMR ( $\delta$  ppm in  $\text{CD}_3\text{OD}$ ): 0.2-1.7 (8H, m), 3.0-3.2 (1H, m), 3.45 (1H, dd,  $J = 7.2$  &  $18.0$  Hz), 3.61 (1H, dd,  $J = 4.0$  &  $14.2$  Hz), 3.87 (1H, dd,  $J = 7.2$  &  $24.6$  Hz), 4.2-4.4 (1H, m), 7.3-8.3 (13H, m), 8.74 (1H, t,  $J = 8.6$  Hz)

Example 119 through 149

The same procedure as in Example 98 was followed to yield the compounds listed in Table 10.

Table 10

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Table 10

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation $[\alpha]_D$ (c, solvent)
119	PhCH <sub>2</sub> OCO-Gly-	131-132	ether-hexane	-16.1° (0.50, CH <sub>3</sub> OH)
120	tBuOCO-Phe-	85-86	Ethyl acetate-hexane	+17.4° (0.71, CHCl <sub>3</sub> )
121	1-Nap-SO <sub>2</sub> -Phe-	85-86 (dec.)	Ethyl acetate-isopropyl ether	-71.5° (0.745, CHCl <sub>3</sub> )
122	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	142-144	Ethyl acetate-isopropyl ether	+14.1° (0.57, CHCl <sub>3</sub> )
123	PhCH <sub>2</sub> CH <sub>2</sub> CO-	124-125	CH <sub>2</sub> Cl <sub>2</sub> -ether	+60.0° (0.58, CHCl <sub>3</sub> )
124	1-Nap-SO <sub>2</sub> -Ala-	119-120 (dec.)	ether	+26.7° (0.50, CH <sub>3</sub> OH)
125	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Ala-	141-142	ether	-52.6° (0.715, CH <sub>3</sub> OH)
126	PhCH <sub>2</sub> OCO-Trp-	86-88	Ethyl acetate-isopropyl ether	-7.6 (0.715, CHCl <sub>3</sub> )
127	tBuOCO-Trp-	95-97	ether-hexane	-23.0° (0.68, DMSO)
128	PhCO-Phe-	113-115 (dec.)	DMF-H <sub>2</sub> O	-55.9° (0.78, DMSO)
129	(PhS)(C <sub>3</sub> H <sub>7</sub> )CHCO-	111-112	CH <sub>2</sub> Cl <sub>2</sub> -ether	+106.6° (0.52, CHCl <sub>3</sub> )
130	PhCH <sub>2</sub> NHCS-Ile-	130-131	Ethyl acetate-isopropyl ether	-12.9° (0.34, DMSO)
131	1-Nap-NHCO-Ile-	192-193 (dec.)	Ethyl acetate-hexane	+4.4° (0.395, DMSO)
132	PhCH <sub>2</sub> OCO-Val-	98-99	ether-hexane	-34.4° (0.50, CH <sub>3</sub> OH)
133	1-Nap-SO <sub>2</sub> -Val-	117-118	ether-hexane	-17.2° (0.50, CH <sub>3</sub> OH)
134	PhCO-Val-	120-121	ether-hexane	-26.9° (0.50, CH <sub>3</sub> OH)

Table 10 (continued)

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
135	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Val-	149-150	Ethyl acetate-hexane	-48.8° (0.50, CH <sub>3</sub> OH)
136	(2-benzimidazolyl-S) (C <sub>3</sub> H <sub>7</sub> )CHCO-	119-120	CH <sub>2</sub> Cl <sub>2</sub> -ether	-28.4° (0.25, CH <sub>3</sub> OH)
137	PhNHCS-Ile-	- <sup>1)</sup>	-	+18.8° (0.485, CHCl <sub>3</sub> )
138	1-Nap-NHCS-Ile-	- <sup>2)</sup>	-	+34.2° (0.325, CHCl <sub>3</sub> )
139	PhCO-Gly	- <sup>3)</sup>	-	-11.0° (0.50, CH <sub>3</sub> OH)
140	PhCH <sub>2</sub> OCO-Ala-	120-121	ether	+22.9° (0.50, CHCl <sub>3</sub> )
141	PhCH <sub>2</sub> OCO-Leu-	- <sup>4)</sup>	-	+15.4° (0.50, CHCl <sub>3</sub> )
142	1-Nap-SO <sub>2</sub> -Leu-	81-82	Ethyl acetate-hexane	-40.5° (0.50, CHCl <sub>3</sub> )
143	PhCO-Leu-	162-163	Ethyl acetate-hexane	-30.4° (0.50, CH <sub>3</sub> OH)
144	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Leu-	107-108	Ethyl acetate-hexane	+2.6° (0.50, CHCl <sub>3</sub> )
145	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Gly-	68-69	Ethyl acetate-hexane	+42.8° (0.50, CHCl <sub>3</sub> )
146	PhCO-Ile-	188-190	Ethyl acetate-hexane	+45.4° (0.26, CHCl <sub>3</sub> )
147	Ph(CH <sub>2</sub> ) <sub>3</sub> CO-	- <sup>5)</sup>	-	-17.4° (0.665, CHCl <sub>3</sub> )
148	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Phe-	141-142	Ethyl acetate-hexane	-19.1° (0.50, CH <sub>3</sub> OH)
149	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-Ile-	143-144	Ethyl acetate-hexane	-41.7° (0.50, CH <sub>3</sub> OH)

DMSO: dimethyl sulfoxide, DMF: N,N-dimethylformamide, Ph: phenyl, 1-Nap: 1-naphtyl, tBu: tert.butyl,  
 5 Ile:(L)-isoleucine, Leu:(L)-leucine, Ala:(L)-alanine, Gly: glycine, Val: (L)-valine, Trp: (L)-tryptophan, Phe: (L)-phenylalanine,

Note 1) Amorphous solid

10 NMR (δ ppm in CDCl<sub>3</sub>): 0.8-1.2 (7H,m), 1.3-1.5 (1H,m), 1.8-2.0 (1H,m), 3.23 (1H,dd,J = 6.6&15.0Hz), 3.34 (1H,dd,J = 6.0&15.0Hz), 4.77 (1H,q,J = 6.6&13.0Hz), 4.91 (1H,t,J = 8.0Hz), 6.65 (1H,d,J = 6.6Hz), 6.73 (1H,d,J = 8.4Hz), 7.0-7.4 (9H,m), 7.57 (1H,d,J = 8.4Hz), 8.18 (1H,broad s), 9.60 (1H,s).

Note 2) Amorphous solid

20 NMR (δ ppm in CDCl<sub>3</sub>): 0.6-1.3 (8H,m), 1.7-1.9 (1H,m), 3.26 (2H,dd,J = 4.8&6.4Hz), 4.70 (1H,q,J = 6.6&13.0Hz), 4.88 (1H,t,J = 8.4Hz), 6.23 (1H,d,J = 8.4Hz), 6.62 (1H,d,J = 7.0Hz), 7.1-8.3 (14H,m), 9.58 (1H,s).

Note 3) Amorphous solid

25 NMR (δ ppm in CDCl<sub>3</sub>): 3.30 (2H,d,J = 7.0Hz), 4.07 (2H,d,J = 5.0Hz), 4.76 (1H,q,J = 7.0Hz), 6.98 (1H,d,J = 2.0Hz), 7.01 (1H,s), 7.07 (1H,dt,J = 1.0&8.0Hz), 7.17 (1H,dt,J = 1.0&8.0Hz), 7.30 (1H,t,J = 7.0Hz), 7.41 (1H,t,J = 7.0Hz), 7.43 (1H,d,J = 7.0Hz), 7.45 (2H,d,J = 8.0Hz), 7.54 (1H,d,J = 7.0Hz), 7.73 (2H,d,J = 8.0Hz), 8.28 (1H,s), 9.61 (1H,s).

Note 4) Amorphous solid

35 NMR (δ ppm in CDCl<sub>3</sub>): 0.89 (6H,d,J = 6.0Hz), 1.45-1.50 (1H,m), 1.56-1.66 (2H,m), 3.28 (2H,t,J = 7.0Hz), 4.18-4.28(1H,m), 4.74 (1H,q,J = 6.0Hz), 5.04 (2H,s), 5.12 (1H,d,J = 9.0Hz), 6.68 (1H,d,J = 6.0Hz), 6.95 (1H,s), 7.11 (1H,dt,J = 1.0&7.0Hz), 7.19 (1H,dt,J = 1.0&7.0Hz), 7.31 (1H,d,J = 1.0Hz), 7.34 (5H,s), 7.57 (1H,d,J = 8.0Hz), 8.08 (1H,s), 9.60 (1H,s).

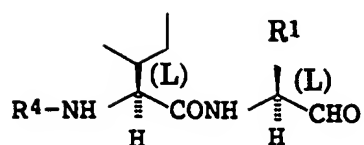
Note 5) Amorphous solid

45 NMR (δ ppm in CDCl<sub>3</sub>): 1.93 (2H,quintet,J = 7.6Hz), 2.18 (2H,t,J = 7.6Hz), 2.61 (2H,t,J = 7.6Hz), 3.24 (1H,dd,J = 15.0&7.0Hz), 3.38 (1H,dd,J = 15.0&5.4Hz), 4.83 (1H,m), 6.03 (1H,d,J = 4.0Hz), 6.90-7.30 (8H,m), 7.60 (1H,d,J = 7.8Hz), 8.19 (1H,broad s), 9.62 (1H,s).

55 Examples 150 through 164

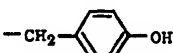
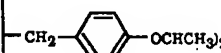
The same procedure as in Example 98 was followed to yield the compounds listed in Table 11.

Table 11



Example No	R <sup>4</sup>	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
150	tBuOCO-		107-108	Ethyl acetate-hexane	-25.7° (0.49, DMSO)
151	PhCH <sub>2</sub> OCO-	-CH <sub>3</sub>	164-165	Ethyl acetate	-26.7° (0.305, DMSO)
152	PhCH <sub>2</sub> OCO-	-CH <sub>2</sub> Ph	138-139	Ethyl acetate-hexane	-47.4° (0.34, DMSO)
153	1-Nap-SO <sub>2</sub> -	-CH <sub>3</sub>	150-151	Ethyl acetate-hexane	+36.7° (0.45, DMSO)
154	1-Nap-SO <sub>2</sub> -	-CH <sub>2</sub> Ph	138-139	Ethyl acetate-hexane	-24.3° (0.595, DMSO)
155	PhCH <sub>2</sub> OCO-		81-82	Ethyl acetate-hexane	+27.7° (0.33, CHCl <sub>3</sub> )
156	PhCH <sub>2</sub> OCO-		103-104	Ethyl acetate-hexane	-40.0° (0.37, DMSO)
157	PhCH <sub>2</sub> OCO-		155-156	Ethyl acetate-hexane	-44.6° (0.315, DMSO)

Table 11 (continued)

Example No	R <sup>4</sup>	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
158	1-Nap-SO <sub>2</sub> -		-1)	-	-20.4° (0.305, CHCl <sub>3</sub> )
159	1-Nap-SO <sub>2</sub> -		117-118	Ethyl acetate-hexane	-16.4° (0.45, DMSO)
160	PhCH <sub>2</sub> OCO-	-CH(CH <sub>3</sub> ) <sub>2</sub>	122-123	Ethyl acetate-hexane	+4.2° (0.29, DMSO)
161	PhCH <sub>2</sub> OCO-	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	157-158	Ethyl acetate-hexane	-29.5° (0.35, DMSO)
162	1-NapSO <sub>2</sub> -	-CH(CH <sub>3</sub> ) <sub>2</sub>	145-146	Ethyl acetate-hexane	+24.3° (0.515, DMSO)
163	1-NapSO <sub>2</sub> -	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	155-156	Ethyl acetate-hexane	+12.9° (0.82, DMSO)
164	PhCH <sub>2</sub> OCO-	H	169-171	Ethyl acetate-hexane	-10.5° (0.50, CHCl <sub>3</sub> )

DMSO: dimethyl sulfoxide, Ph: phenyl, 1-Nap: 1-naphthyl, tBu: tert.butyl,

Note 1) Amorphous solid

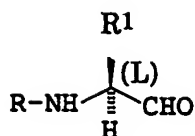
NMR (δ ppm in CDCl<sub>3</sub>): 0.4-0.7 (6H,m), 0.7-1.0 (1H,m), 1.0-1.2 (1H,m), 1.5-1.8 (1H,m), 2.58 (1H,dd,J=7.0&14.0Hz), 2.74 (1H,dd,J=6.6&14.0Hz), 3.59 (1H,dd,J=5.6&7.8Hz), 4.38 (1H,q,J=6.6&13.6Hz), 5.81 (1H,d,J=8.0Hz), 6.5-7.0 (6H,m), 7.4-7.7 (3H,m), 7.91 (1H,d,J=8.0Hz), 8.05 (1H,d,J=8.0Hz), 8.23 (1H,d,J=7.4Hz), 8.68 (1H,d,J=8.0Hz), 9.16 (1H,s).

Examples 165 through 169

The same procedure as in Example 98 was followed to yield the compounds listed in Table 12.



Table 12



Example No	R	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
165	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH <sub>2</sub> Ph	113-114	CH <sub>2</sub> Cl <sub>2</sub> -isopropyl ether	+ 29.0° (0.59, CHCl <sub>3</sub> )
166	PhCH <sub>2</sub> OCO-Leu-Leu-	H	110-111	Ethyl acetate-hexane	-51.2° (0.50, CH <sub>3</sub> OH)
167	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH <sub>2</sub> CH <sub>3</sub>	141-142	CH <sub>2</sub> Cl <sub>2</sub> -hexane	+ 19.3° (0.51, CHCl <sub>3</sub> )
168	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH(CH <sub>3</sub> ) <sub>2</sub>	139-140	CH <sub>2</sub> Cl <sub>2</sub> -hexane	+ 40.4° (0.53, CHCl <sub>3</sub> )
169	(PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	-CH <sub>3</sub>	136-137	CH <sub>2</sub> Cl <sub>2</sub> -hexane	-3.9° (0.55, CHCl <sub>3</sub> )

Leu: (L)-leucine, Ph: phenyl

#### Example 170

The same procedure as in Example 98 was followed to yield N-benzyloxycarbonyl-(L)-isoleucyl-(D)-tryptophanal and recrystallized from ethyl acetate-hexane. Melting point 163-164 °C.  
[α]<sub>D</sub> +37.2° (c0.635, DMSO)

#### Example 171

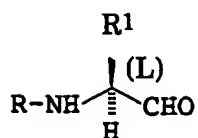
The same procedure as in Example 98 was followed to yield N-(1-naphthylsulfonyl)-(L)-isoleucyl-(D)-tryptophanal as an amorphous solid.  
[α]<sub>D</sub> -39.3° (c0.30, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (δ ppm in CDCl<sub>3</sub>): 0.50 (3H,d,J=6.8Hz), 0.62 (3H,t,J = 7.6Hz), 0.7-0.9 (1H,m), 1.2-1.4 (1H,m), 1.5-1.8 (1H,m), 2.90 (1H,dd,J=7.4&14.8Hz), 3.12 (1H,dd,J=8.0&14.8Hz), 3.53 (1H,dd,J=5.4&7.8Hz), 4.36 (1H,dd,J=6.2&13.0Hz), 5.47 (1H,d,J=8.0Hz), 6.50 (1H,d,J=6.6Hz), 7.0-8.3 (12H,m), 8.63 (1H,d,J=8.4Hz), 9.19 (1H,s).

#### Examples 172 through 193

The same procedure as in Example 98 was followed to yield the compounds listed in Table 13 and 14.

Table 13



Example No	R	R <sup>1</sup>	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
172	(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> CHCO-	PhCH <sub>2</sub> -	108-109	CH <sub>2</sub> Cl <sub>2</sub> -ether-isopropyl ether	+88.9° (0.5, CHCl <sub>3</sub> )
173	Ph(CH <sub>2</sub> ) <sub>3</sub> CO-	PhCH <sub>2</sub> -	112-113	AcOEt-ether-hexane	+53.7° (0.535, CHCl <sub>3</sub> )
174	PhCH <sub>2</sub> OCO-Leu-	H	93-94	AcOEt-hexane	+2.6° (0.23, CHCl <sub>3</sub> )
175	1-Nap-SO <sub>2</sub> -Leu-Trp-	H	177-178	AcOEt	-13.1° (0.235, DMSO)

Leu: (L)-leucine, Trp: (L)-tryptophan, Ph: phenyl, 1-Nap: 1-naphthyl, AcOEt: ethyl acetate

Table 14

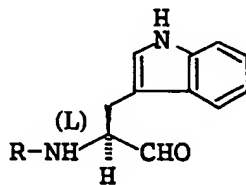


Table 14

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
176	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> CO-	50-51	AcOEt-hexane	-34.1° (0.5, CH <sub>3</sub> OH)
177	cyclohexyl-CO-	138-139	AcOEt-hexane	-41.5° (0.5, CH <sub>3</sub> OH)
178	Ph-CO-	134-135	AcOEt-hexane	-97.2° (0.5, CH <sub>3</sub> OH)
179	Ph(C <sub>2</sub> H <sub>5</sub> )CH-CO-	— <sup>1)</sup>	AcOEt-hexane	+12.6 (0.585, CHCl <sub>3</sub> )
180	(PhCH <sub>2</sub> )[(4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ]CH-CO-	— <sup>2)</sup>		+32.3° (0.475, CHCl <sub>3</sub> )
181	PhCH <sub>2</sub> CH <sub>2</sub> -CO-Val-	161-162	AcOEt-hexane	-72.1° (0.50, CH <sub>3</sub> OH)
182	(PhCH <sub>2</sub> ) <sub>2</sub> CH-CO-Val-	156-157	AcOEt-hexane	-44.0° (0.50, CH <sub>3</sub> OH)
183	(PhCH <sub>2</sub> )[(2-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ]CH-CO-	136-138	AcOEt-hexane	+15.5° (0.475, CHCl <sub>3</sub> )
184	(PhCH <sub>2</sub> )[(4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> ]CH-CO-	— <sup>3)</sup>		+15.7° (0.54, CHCl <sub>3</sub> )
185	[(4-PhCONH-C <sub>6</sub> H <sub>4</sub> )-CH <sub>2</sub> ](PhCH <sub>2</sub> )CH-CO-	190-191	AcOEt-hexane	-69.9° (0.405, CHCl <sub>3</sub> )
186	[(4-CH <sub>3</sub> CONH-C <sub>6</sub> H <sub>4</sub> )-CH <sub>2</sub> ](PhCH <sub>2</sub> )CH-CO-	124-125	AcOEt-hexane	-32.4° (0.225, DMSO)
187	[(4-Tol-SO <sub>2</sub> NH-C <sub>6</sub> H <sub>4</sub> )-CH <sub>2</sub> ](PhCH <sub>2</sub> )CH-CO-	— <sup>4)</sup>		+22.2° (0.415, CHCl <sub>3</sub> )
188	[[4-(C <sub>2</sub> H <sub>5</sub> O) <sub>2</sub> P(O)-CH <sub>2</sub> ]C <sub>6</sub> H <sub>4</sub> NHCO](PhCH <sub>2</sub> )CH-CO-	— <sup>5)</sup>		-5.8° (0.665, CHCl <sub>3</sub> )
189	(C <sub>2</sub> H <sub>5</sub> OOC)(PhCH <sub>2</sub> )CH-CO-	— <sup>6)</sup>		+22.3° (0.66, CHCl <sub>3</sub> )
190	[(PhCH <sub>2</sub> ) <sub>2</sub> N-CO](PhCH <sub>2</sub> ) <sub>2</sub> CHCO-	— <sup>7)</sup>		+6.6° (0.90, CHCl <sub>3</sub> )
191	(PhCH <sub>2</sub> NH-CO)(PhCH <sub>2</sub> )CHCO-	— <sup>8)</sup>		-14.2° (0.94, DMSO)

Table 14 (continued)

Example No.	R	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
192	Ph <sub>2</sub> CH-CO-	172-173	AcOEt-hexane	-8.0° (0.37, DMSO)
193	(4-oxo-4H-1-benzopyran-2-yl)-CO-Ile-	120-121	AcOEt-hexane	-69.8° (0.50, CH <sub>3</sub> OH)

Leu: (L)-leucine, Val: (L)-valine, Ph: phenyl, Tol: 4-tolyl, AcOEt: ethyl acetate

Note 1) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 0.86 (3H,t,J=7.4Hz), 1.80 (1H,m), 2.17 (1H,m), 3.13-3.37 (3H,m), 4.64 (1H,q,J=6.6Hz), 6.06 (1H,d,J=5.8Hz), 6.75 (1H,d,J=2.0Hz), 7.00-7.40 (7H,m), 7.55 (1H,d,J=7.8Hz), 8.07 (1H,broad s), 9.53 (1H,s).

Note 2) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 2.27&2.30 (3H,each s), 2.46-2.66 (1H,m), 2.72-3.24 (6H,m), 5.53-5.70 (1H,m), 6.37-6.52 (1H,m), 6.88-7.50 (13H,m), 7.95 (1H,broad), 9.19&9.21 (1H,each s).

Note 3) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 2.35-3.20 (7H,m), 3.75&3.77 (3H,each s), 4.42-4.58 (1H,m), 5.50-5.62 (1H,m), 6.32&6.38 (1H,each d,J=2.4Hz), 6.72-6.88 (2H,m), 7.00-7.60 (11H,m), 7.92 (1H,broad s), 9.19&9.25 (1H,each broad s).

Note 4) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 2.30 (3H,s), 2.5-3.1 (7H,m), 4.2-4.4 (1H,m), 5.72 (1H,d,J=6.6Hz), 6.25 (1H,d,J=1.8Hz), 6.8-7.4 (15H,m), 7.59 (2H,d,J=8.2Hz), 8.32 (1H,broad s), 9.13 (1H,s).

Note 5) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 1.21 (3H,t,J=7.0Hz), 1.22 (3H,t,J=7.0Hz), 3.0-3.3 (6H,m), 3.5-3.7 (1H,m), 3.8-4.1 (4H,m), 4.5-4.7 (1H,m), 6.65&6.71 (1H,each d,J=1.6Hz), 7.0-7.6 (13H,m), 8.44&8.61 (1H,each broad s), 9.27&9.39 (1H,each broad s), 9.42&9.47 (1H,each s).

## Note 6) Oil

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 1.12 (3H,t,J=6.2Hz), 3.1-3.6 (5H,m), 4.02 (2H,q,J=14.2&6.2Hz), 4.6-4.8 (1H,m), 6.81&6.92 (1H,each d,J=2.2Hz), 7.0-7.4 (9H,m), 7.49&7.59 (1H,each d,J=7.4Hz), 8.22 (1H,broad s), 9.51&9.54 (1H,each s).

## Note 7) Amorphous solid

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 3.0-3.4 (4H,m), 3.85 (1H,dt,J=10.4&4.2Hz), 4.0-4.5 (4H,m), 4.6-4.8 (1H,m), 6.6-6.8 (2H,m), 6.9-7.3 (17H,m), 7.4-7.7 (2H,m), 8.33&8.38 (1H,each s), 9.56 (1H,s).

## Note 8) Amorphous solid

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 2.9-3.3 (4H,m), 3.54 (1H,t,J=7.2Hz), 4.0-4.5 (3H,m), 6.9-7.5 (15H,m), 8.23 (1H,d,J=7.0Hz), 8.29 (1H,t,J=7.0Hz), 9.43&9.47 (1H,each s), 10.86 (1H,s).

## Example 194

To a solution of N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanol (1.0 g) and acetyl chloride (0.171 g) in N,N-dimethylformamide (6 ml) was added 4-(N,N-dimethylamino)pyridine (0.28 g) under ice-cooling and stirred for 3 hours at the same temperature. The reaction mixture was poured on ice-water and extracted with ethyl acetate. The ethyl acetate layer was washed sequentially with an aqueous citric acid solution, water, an aqueous sodium bicarbonate solution and water, and dried ( $\text{MgSO}_4$ ). After the solvent was distilled off, the residue was subjected to silica gel column chromatography. O-acetyl compound of N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanol (shown as Example No. 194 in Table 16) was obtained as an amorphous solid (0.83 g, 76%) from the eluted fraction of ethyl acetate-hexane (2:3, v/v).

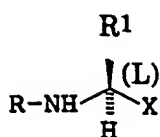
NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 0.5-0.9 (7H,m), 1.0-1.2 (1H,m), 1.6-1.8 (1H,m), 2.01 (3H,s), 2.53 (1H,dd,J = 14.8&6.2Hz), 2.63 (1H,dd,J = 14.8&7.0Hz), 3.52 (1H,dd,J = 8.2&5.2Hz), 3.68 (1H,dd,J = 11.4&6.4Hz), 3.79 (1H,dd,J = 11.4&6.6Hz), 4.1-4.3 (1H,m), 5.55 (1H,d,J = 8.2Hz), 6.10 (1H,d,J = 8.4Hz), 6.91 (1H,d,J = 2.2Hz), 7.0-7.7 (7H,m), 7.89 (1H,d,J = 8.4Hz), 8.02 (1H,d,J = 8.2Hz), 8.22 (1H,dd,J = 7.2&1.2Hz), 8.29 (1H,broad s), 8.67 (1H,d,J = 8.4Hz).  $[\alpha]_D^{25} -31.4^\circ$  (c 0.39,  $\text{CHCl}_3$ ).

Elemental analysis (for $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_5\text{S} \cdot 1/2\text{H}_2\text{O}$ )			
Calcd.	C, 63.95;	H, 6.29;	N, 7.71
Found	C, 64.17;	H, 6.20;	N, 7.55

## Example 195 through 198

The same procedure as in Example 194 was followed to yield the compounds listed in Table 15.

Table 15



Example No	R	R <sup>1</sup>	X	Melting Point (°C)	Recrystallization Solvent	Optical Rotation [α] <sub>D</sub> (c, solvent)
194	1-Nap-SO <sub>2</sub> -Ile-	3-Ind-CH <sub>2</sub> -	-CH <sub>2</sub> OCO-CH <sub>3</sub>	—		-31.3° (0.39, CHCl <sub>3</sub> )
195	1-Nap-SO <sub>2</sub> -Ile-	3-Ind-CH <sub>2</sub> -	-CH <sub>2</sub> OCO-CH <sub>2</sub> CH <sub>3</sub>	— <sup>1)</sup>		-27.8° (0.52, CHCl <sub>3</sub> )
196	1-Nap-SO <sub>2</sub> -Ile-	3-Ind-CH <sub>2</sub> -	-CH <sub>2</sub> OCO-Ph	— <sup>2)</sup>		-11.3° (0.435, CHCl <sub>3</sub> )
197	(PhCH <sub>2</sub> ) <sub>2</sub> C HCO-	3-Ind-CH <sub>2</sub> -	-CH <sub>2</sub> OCO-CH <sub>3</sub>	129-130	AcOEt-hexane	-7.2° (0.75, DMSO)
198	1-Nap-SO <sub>2</sub> -Leu-Trp-	CH <sub>3</sub> -	-CH <sub>2</sub> OCO-CH <sub>3</sub>	157-158	AcOEt-hexane	+55.9° (0.705, DMSO)

1-Nap: 1-naphthyl, Ile: (L)-isoleucine, Trp: (L)-tryptophan Ph: phenyl, 3-Ind: 3-indolyl, AcOEt: ethyl acetate

Note 1) Amorphous solid

NMR (δ ppm in CDCl<sub>3</sub>): 0.5-0.9 (7H,m), 1.00 (3H,t,J=7.6Hz), 1.0-1.2 (1H,m), 1.5-1.8 (1H,m), 2.28 (2H,q,J=7.6Hz), 2.51 (1H,dd,J=14.6&6.2Hz), 2.61 (1H,dd,J=14.6&7.2Hz), 3.53 (1H,dd,J=8.0&5.4Hz), 3.68 (1H,dd,J=11.4&6.2Hz), 3.79 (1H,dd,J=11.4&4.8Hz), 4.1-4.3 (1H,m), 5.64

(1H,d,J=8.0Hz), 6.14 (1H,d,J=8.4Hz), 6.90 (1H,d,J=2.0Hz), 7.0-7.7 (7H,m),  
7.88 (1H,d,J=7.8Hz), 8.01 (1H,d,J=8.2Hz), 8.21 (1H,d,J=7.2Hz), 8.38  
5 (1H,broad s), 8.67 (1H,d,J=8.4Hz).

Note 2) Amorphous solid

NMR ( $\delta$  ppm in  $\text{CDCl}_3$ ): 0.50 (3H,t,J=7.2Hz), 0.59 (3H,d,J=6.8Hz),  
10 0.6-0.9 (1H,m), 1.0-1.2 (1H,m), 1.5-1.8 (1H,m), 2.53 (1H,dd,J=14.6&6.2Hz),  
2.64 (1H,dd,J=14.6&7.2Hz), 3.57 (1H,dd,J=8.4&5.4Hz), 3.87  
(1H,dd,J=11.4&6.8Hz), 3.97 (1H,dd,J=11.4&4.6Hz), 4.2-4.4 (1H,m), 5.70  
15 (1H,d,J=8.4Hz), 6.19 (1H,d,J=8.4Hz), 6.91 (1H,d,J=2.4Hz), 7.0-7.6 (10H,m),  
7.8-8.0 (4H,m), 8.17 (1H,dd,J=7.4&1.0Hz), 8.40 (1H,broad s), 8.67  
(1H,d,J=8.6Hz).

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(i) APPLICANT:

- (A) NAME: Takeda Chemical Industries, Ltd.
- (B) STREET: 1-1, Doshomachi 4-chome
- (C) CITY: Chuo-ku, Osaka
- (E) COUNTRY: Japan
- (F) POSTAL CODE (ZIP): 541

10

(ii) TITLE OF INVENTION: Alcohol or Aldehyde Derivatives and Their Use

(iii) NUMBER OF SEQUENCES: 5

15

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

20

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: NO

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

TTTTCAGGGG GCAGTAAGAT

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(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

40

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: NO

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

CCGGATCCGG CTTTTTAGGA TTGGTCTA

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## (2) INFORMATION FOR SEQ ID NO: 3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (iii) ANTI-SENSE: YES

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GGGGGCTGGT AGACTGAAGA

## (2) INFORMATION FOR SEQ ID NO: 4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (iii) ANTI-SENSE: YES

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

CCGGATCCAT TCCTCCCATG CATGCGCC

## (2) INFORMATION FOR SEQ ID NO: 5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

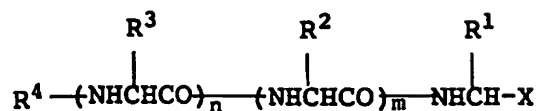
## (iii) ANTI-SENSE: NO

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

CCCGGATCCG GG

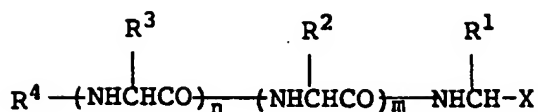
## Claims

1. A cathepsin L inhibitor containing a compound of the formula:



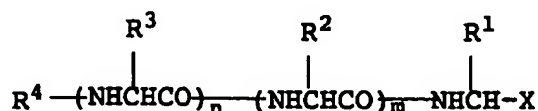
wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group which may be substituted; R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom or a hydrocarbon residue which may be substituted; R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group which may be substituted; X is formula: -CHO or -CH<sub>2</sub>OB (wherein B is a hydrogen atom or a protecting group of hydroxy group); m and n independently are an integer of 0 or 1; provided that R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl, or a carbamoyl or thiocarbamoyl group which may be substituted when R<sup>1</sup> is an unsubstituted lower alkyl, arylalkyl or methylthioethyl group, R<sup>2</sup> and R<sup>3</sup> independently are a lower alkyl or arylalkyl, X is -CHO, m is 1 and n is 0 or 1, or a salt thereof.

- 10 2. The cathepsin L inhibitor according to claim 1 wherein R<sup>1</sup> is an indolyl-lower alkyl.
3. The cathepsin L inhibitor according to claim 1 wherein R<sup>1</sup> is a naphthyl-lower alkyl.
- 15 4. The cathepsin L inhibitor according to claim 1 wherein R<sup>1</sup> is a phenyl-lower alkyl.
5. The cathepsin L inhibitor according to claim 1 wherein R<sup>1</sup> is a hydrogen or lower alkyl.
6. The cathepsin L inhibitor according to claim 1 wherein R<sup>2</sup> is a branched lower alkyl.
- 20 7. The cathepsin L inhibitor according to claim 1 wherein R<sup>2</sup> is a phenyl-lower alkyl.
8. The cathepsin L inhibitor according to claim 1 wherein R<sup>3</sup> is a branched lower alkyl.
- 25 9. The cathepsin L inhibitor according to claim 1 wherein R<sup>3</sup> is a hydrogen.
10. The cathepsin L inhibitor according to claim 1 wherein R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group substituted by an alkyl, aryl, arylalkyl or alicyclic hydrocarbon group.
- 30 11. The cathepsin L inhibitor according to claim 10, wherein R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl, or a carbamoyl or thiocarbamoyl group which may be substituted.
12. The cathepsin L inhibitor according to claim 1, wherein X is -CHO or -CH<sub>2</sub>OH.
- 35 13. The cathepsin L inhibitor according to claim 1, wherein m is 1 and n is 1.
14. The cathepsin L inhibitor according to claim 1, wherein m is 1 and n is 0.
- 40 15. The cathepsin L inhibitor according to claim 1, wherein m is 0 and n is 0.
16. The cathepsin L inhibitor according to claim 1, wherein R<sup>1</sup> is a lower alkyl which may be substituted by indolyl; R<sup>2</sup> is a lower alkyl; R<sup>4</sup> is a naphthylsulfonyl or dibenzylacetyl; X is -CHO or -CH<sub>2</sub>OH; m is 0 or 1 and n is 0.
- 45 17. The cathepsin L inhibitor according to claim 1, which contains N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanal.
18. The cathepsin L inhibitor according to claim 1, which contains N-dibenzylacetyl-(L)-tryptophanal.
- 50 19. The cathepsin L inhibitor according to claim 1, which contains N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-alaninal.
20. The cathepsin L inhibitor according to claim 1, which contains N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanol.
- 55 21. A bone resorption inhibitor containing a compound of the formula:



wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group which may be substituted; R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom or a hydrocarbon residue which may be substituted; R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group which may be substituted; X is formula: -CHO or -CH<sub>2</sub>OB (wherein B is a hydrogen atom or a protecting group of hydroxyl group); m and n independently are an integer of 0 or 1; provided that R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl, or a carbamoyl or thiocarbamoyl group which may be substituted when R<sup>1</sup> is an unsubstituted lower alkyl, arylalkyl or methylthioethyl group, R<sup>2</sup> and R<sup>3</sup> independently are a lower alkyl or arylalkyl, X is -CHO, m is 1 and n is 0 or 1, or a salt thereof.

22. A compound of the formula:



wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group which may be substituted; R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom or a hydrocarbon residue which may be substituted; R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group which may be substituted; X is formula: -CHO or -CH<sub>2</sub>OB (wherein B is a hydrogen atom or a protecting group of hydroxyl group); m and n independently are an integer of 0 or 1; provided that R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl, or a carbamoyl or thiocarbamoyl group which may be substituted when R<sup>1</sup> is an unsubstituted lower alkyl, arylalkyl or methylthioethyl group, R<sup>2</sup> and R<sup>3</sup> independently are a lower alkyl or arylalkyl, X is -CHO, m is 1 and n is 0 or 1, or a salt thereof.

23. The compound according to claim 22 wherein R<sup>1</sup> is an indolyl-lower alkyl.

24. The compound according to claim 22 wherein R<sup>1</sup> is a naphthyl-lower alkyl.

25. The compound according to claim 22 wherein R<sup>1</sup> is a phenyl-lower alkyl.

26. The compound according to claim 22 wherein R<sup>1</sup> is a hydrogen or lower alkyl.

27. The compound according to claim 22 wherein R<sup>2</sup> is a branched lower alkyl.

28. The compound according to claim 22 wherein R<sup>2</sup> is a phenyl-lower alkyl.

29. The compound according to claim 22 wherein R<sup>3</sup> is a branched lower alkyl.

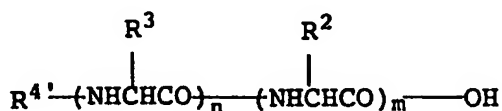
30. The compound according to claim 22 wherein R<sup>3</sup> is a hydrogen.

31. The compound according to claim 22 wherein R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, carbamoyl or thiocarbamoyl group substituted by an alkyl, aryl, arylalkyl or alicyclic hydrocarbon group.

32. The compound according to claim 31, wherein R<sup>4</sup> is an alkanoyl group substituted by aryl, a sulfonyl group substituted by aryl having more than 9 carbon atoms or by lower alkyl, or a carbamoyl or thiocarbamoyl group which may be substituted.

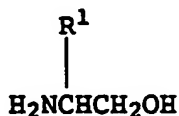
33. The compound according to claim 22, wherein X is -CHO or -CH<sub>2</sub>OH.

34. The compound according to claim 22, wherein m is 1 and n is 1.
35. The compound according to claim 22, wherein m is 1 and n is 0.
- 5 36. The compound according to claim 22, wherein m is 0 and n is 0.
37. The compound according to claim 22, wherein R<sup>1</sup> is a lower alkyl which may be substituted by indolyl; R<sup>2</sup> is a lower alkyl; R<sup>4</sup> is a naphthylsulfonyl or dibenzylacetyl; X is -CHO or -CH<sub>2</sub>OH; m is 0 or 1 and n is 0.
- 10 38. The compound according to claim 22, which is N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanal.
39. The compound according to claim 22, which is N-dibenzylacetyl-(L)-tryptophanal.
- 15 40. The compound according to claim 22, which is N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-alaninal.
41. The compound according to claim 22, which is N-(1-naphthylsulfonyl)-(L)-isoleucyl-(L)-tryptophanol.
42. A method of producing the compound as defined in claim 22 which comprises reacting a compound of the formula:
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wherein R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom or a hydrocarbon residue which may be substituted, R<sup>4</sup> is an alkanoyl, sulfonyl, carbonyloxy, group which may be substituted, or its reactive derivative with a compound of the formula:

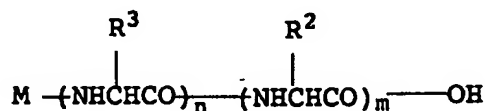
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wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group which may be substituted, and if desired, subjecting to an oxidation reaction or a reaction of protecting a hydroxyl group.

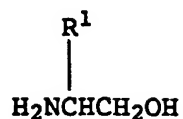
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43. A method of producing the compound as defined in claim 22 which comprises reacting a compound of the formula:
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wherein R<sup>2</sup> and R<sup>3</sup> independently are a hydrogen atom or a hydrocarbon residue which may be substituted, M is a protecting group of amino group, m and n independently are an integer of 0 or 1, or its reactive derivative with a compound of the formula:

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wherein R<sup>1</sup> is a hydrogen atom or an arylalkyl, heterocyclic-alkyl or lower alkyl group, subjecting to deprotecting reaction, to acylation, sulfonylation, oxycarbonylation, carbamoylation or thiocarbamoylation reaction in this order, and if desired, subjecting to an oxidation reaction or a reaction of protecting a hydroxyl group.

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44. A method for prophylaxis or treatment of a mammal suffering from osteoporosis which comprises administering to said mammal an effective amount of the compound according to claim 22.

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45. A use of the compound according to claim 22 for prophylaxis or treatment of a mammal suffering from osteoporosis.

46. A method of producing the pharmaceutical composition according to claim 1 or 2 which comprises admixing the compound defined in said claim with a carrier, excipient or diluent therefor.

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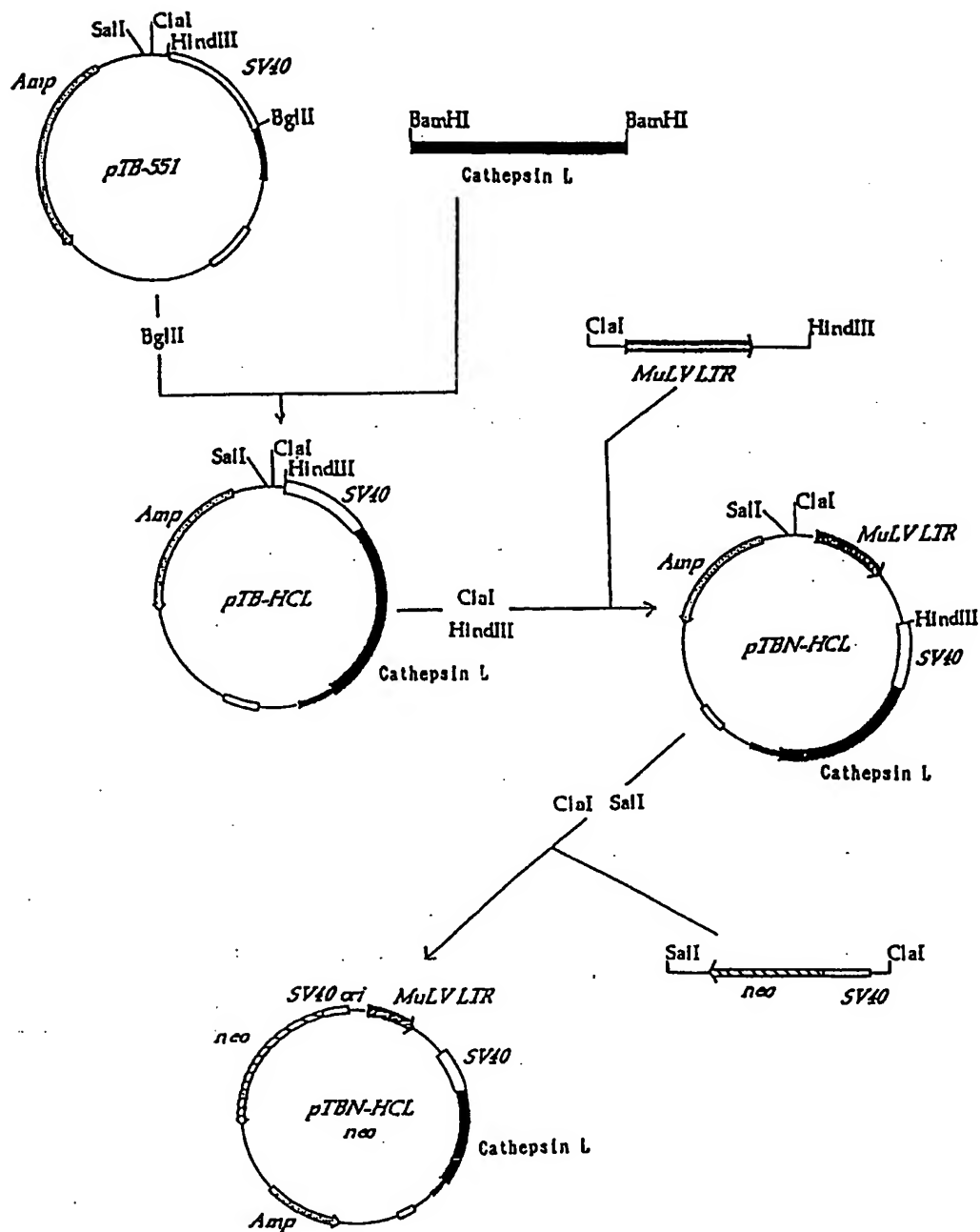


Figure 1